Understanding Determinants of Medication Adherence and Current Adherence Assessment Practices in Australian Haemodialysis Patients

by

Saurav Ghimire (BPharm, MPharm)

Division of Pharmacy, School of Medicine, Faculty of Health

University of Tasmania, Hobart

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STATEMENT OF ETHICAL CONDUCT

The research associated with this thesis abides by the Australian codes on human and animal experimentation, the guidelines by the Australian National Ethics and Institutional Biosafety Committees of the University. All research involving patients undergoing haemodialysis and renal healthcare professionals was conducted under the approval of the Tasmanian Human Research Ethics Committee (Approval numbers H0014506 and H0015433).

Saurav Ghimire

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STATEMENT OF CO-AUTHORSHIP

Given that this thesis is presented as a sequences of papers, either published, in press or submitted, statement of co-authorship are provided for each chapter. Due to this thesis format, some repetition is expected.

The following individuals and organisations contributed to the publication or preparation of the work undertaken as part of this thesis.

Candidate: Saurav Ghimire

Author 1: Syed Tabish R. Zaidi[1]

Author 2: Ronald L. Castelino[1, 2]

Author 3: Gregory M. Peterson[1]

Author 4: Kenneth Lee[1]

Author 5: Matthew D. Jose[3, 4]

Author 6: Colin Banks[4]

Author 7: Nicole M. Lioufas[4]

[1]Pharmacy, School of Medicine, University of Tasmania, Hobart, Australia; [2]Sydney Nursing School, The University of Sydney, Sydney, Australia; [3]School of Medicine, Faculty of Health, University of Tasmania, Hobart, Australia; [4]Department of Nephrology, Royal Hobart Hospital, Hobart, Australia.

PUBLICATIONS

All publications listed resulted from work described in this thesis.

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Located in Chapter 5: *Candidate was the primary author; who in conjunction with authors 1 and 2 conceived and designed the study. Candidate undertook all data collection, analysis and drafting of the manuscript. Authors 1, 2, 5 and 6 provided input into the writing of the research article.*

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4. Ghimire S, Banks C, Castelino RL, Jose MD, Zaidi ST. Current practices of assessing medication adherence in Australian dialysis centres. Australasian Pharmaceutical Science Association (APSA) Annual Conference 2016. Sydney, December 2 to 5, 2016.

We the undersigned agree with the above stated, "proportion of work undertaken" for each of the above published or under review peer-reviewed manuscripts contributing to this thesis:

Signed:

	Dr Syed Tabish R. Zaidi	Prof Ben Canny
	Supervisor	*Head of School*
	School of Medicine	*School of Medicine*
	University of Tasmania	University of Tasmania
Date:	16/03/2018	19/03/2018

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ABBREVIATIONS

Acronym	Definition
ACSQHC	Australian Commission on Safety and Quality in Health Care
ARP	Australasian Renal Pharmacists
BMQ	Beliefs about Medicines Questionnaires
BOT	Burden of Oral Therapy
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CI	Confidence Interval
CCI	Charlson's Comorbidity Index
CKD	Chronic Kidney Diseases
COREQ	Consolidated Criteria for Reporting Qualitative Research
DIPQ	Drug Intake Percentage Questionnaire
DOTS	Directly Observed Treatment, Short Course
EPHPP	Effective Public Health Practice Project
EQ-5D	EuroQol 5 Dimensions Questionnaire
ESKD	End-Stage Kidney Disease
HCP	Healthcare Professionals
HD	Haemodialysis
HR-QoL	Health-related Quality of Life
ITAS-M	Modified Immunosuppressive Therapy Adherence Scale
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KDIGO	Kidney Disease Improving Global Outcomes
KHA-CARI	Kidney Health Australia- Caring for Australasians with Renal Impairment
LC	Lanthanum Carbonate
MAP	Medication Adherence Programs
MAQ	Medication Adherence Questionnaire
MARS	Medication Adherence Report Scale
MEMS	Medication Event Monitoring System
MeSH	Medical Subject Heading

Acronym	Definition
MGLT-4	4-item Morisky Green Levine Test
MMAS-8	8-item Morisky Medication Adherence Scale
MRCI	Medication Regimen Complexity Index
NFK-KDOQI	National Kidney Foundation- Kidney Disease Outcomes Quality Initiative
OR	Odds Ratio
PB	Phosphate Binders
PBM	Perceived Burden of Medicines
PBS	Pharmaceutical Benefits Scheme
PD	Peritoneal Dialysis
PGA	Pharmacy Guild of Australia
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PSR	Patient Self-reports
QUM	Quality Use of Medicines
RSA	Renal Society of Australasia
RN	Registered Nurse
SH	Sevelamer Hydrochloride
SHPA	Society of Hospital Pharmacists of Australia
SMAQ	Simplified Medication Adherence Questionnaire
SPL	Serum Phosphate Levels
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
WHO	World Health Organisation

ABSTRACT

Medication nonadherence is a well-recognised problem in chronic diseases with a global prevalence rate estimated to be 50%. Determinants of nonadherence are multifactorial, although increasing complexity of disease and medication regimen contribute to nonadherence. End-stage kidney disease (ESKD) patients undergoing haemodialysis are prescribed complex regimens and are at high risk of medication nonadherence. Current clinical practice places significant emphasis on selecting medications that have been shown to improve patient outcomes, however little attention is paid to measuring and ensuring patient adherence to their prescribed treatments. Our understanding of factors contributing to medication nonadherence in patients undergoing haemodialysis is limited. This research sought to determine potential predictors of medication nonadherence, explore current practices and barriers to assessing adherence, and identify strategies to improve adherence assessment practices in clinical settings. The specific research objectives were to:

- summarise existing literature on medication nonadherence and identify factors associated with medication nonadherence in patients undergoing haemodialysis;
- investigate the prevalence pattern, and socio-demographic, clinical and psychosocial factors contributing to medication nonadherence in Australian haemodialysis patients, and
- identify current practices of assessing medication adherence in renal patients by health professionals, barriers to assessment, and strategies to improve adherence assessment practices in Australian dialysis centres.

These research aims were investigated in four distinct studies. The first study summarised the existing literature on medication nonadherence using a systematic review. From the 44 relevant publications identified through the systematic review, the prevalence of medication nonadherence in patients undergoing haemodialysis varied between 12.5% and 98.6%. This wide variation occurred due to the heterogeneity in measures and definitions employed by the included studies. This inconsistency in the reporting of results did not allow us to conduct a more effective synthesis of results, such as meta-analysis, as part of the systematic review. However, through a narrative synthesis approach we identified a number of patient-, disease-, and medication-related factors contributing to nonadherence in patients undergoing haemodialysis.

The second study was a prospective study of 53 adult (≥ 18 years) patients undergoing haemodialysis, recruited from an outpatient dialysis centre in Hobart, Australia. More than half (56.6%, n = 30) of these patients were found to be nonadherent based on self-reports. Comparatively, nonadherence was much higher among the subset of patients (n = 33) analysed using pre-dialysis serum phosphate levels, as an objective measure (72.7%, n = 24). Increasing age was the only significant predictor of self-reported adherence (odds ratio (OR) 1.05; 95% CI 1.00–1.11), whereas older age (OR 1.10; 95% CI 1.00–1.21), higher level of comorbidity (OR 1.58; 95% CI 1.03–2.42), and higher medication regimen complexity index (OR 1.14; 95% CI 1.02–1.27) were independent predictors of objective adherence.

The third study was a qualitative study aimed at exploring haemodialysis patients' perspectives on their medication-taking behaviour. Thirty patients undergoing haemodialysis from the aforementioned prospective study, completed one-on-one semi-structured interviews. The qualitative themes identified were mapped against WHO (World Health Organisation) determinants of adherence and comprised of

patient-related (knowledge, awareness, attitude, self-efficacy, action control, and facilitation); health system/healthcare team-related (quality of interaction, and mistrust and collateral arrangements); therapy-related (physical characteristics of medicines, packaging, and side effects); condition-related (symptom severity); and social/economic factors (access to medicines, and relative affordability).

Findings from the second and third study, led to the inception of the fourth study on healthcare professionals' perspectives on the issue of medication nonadherence in patients undergoing haemodialysis. As such, the fourth study consisted of cross-sectional surveys and follow-up interviews with renal healthcare professionals, aimed at measuring their perceptions and practices of assessing adherence in clinical practice. A total of 113 renal nurses and 41 specialist renal pharmacists participated in this study. Attempts to engage renal doctors were unsuccessful despite trying various recruitment strategies. Renal nurses (83.2%, n = 89), relied heavily upon objective blood results to determine adherence, compared to pharmacists (57.1%, n = 16). Patient engagement via self-reported measures were rarely used by the pharmacists (27.6%, n = 8) compared to the nurses (55.1%, n = 59); this was mainly due to absence of a dedicated pharmacist to conduct such activities. Perceived barriers to assessing adherence by the renal professionals included: lack of time, administrative support, and patients' disinterest in discussing medication related issues.

Survey participants were followed-up for a qualitative interview to expand on the survey findings and identify strategies to improve adherence assessment practices. Eighteen participants, comprising 12 nurses and six pharmacists, were interviewed. Three categories of barriers with seven underlying themes were identified: organisation-level (prioritisation of resources), professional-level (interplay between

workload and available time, awareness and training deficits, and concerns around practicality/suitability of adherence tools), and patient-level (communication and assessment services, patient participation, and trust). Similarly, strategies that were identified to improve adherence assessment practices, included: formalisation of assessment process, integration of assessment process and tools into routine, and using multidisciplinary support.

Despite the widespread prevalence of medication nonadherence among Australian haemodialysis patients, little attention has been given to ensuring patients adhere to their prescribed medicines. Communication and dialogue between patients and healthcare providers concerning medication-related issues are lacking within the dialysis settings. In order to improve this status quo, measuring nonadherence is vital. However, renal professionals placed too much emphasis on objective measures while assessing adherence; using such measures is subject to overlooking actual understanding of patient's medication-taking behaviour. As patient self-reported measures are important tools to supplement the objective measures, they should be promoted to healthcare providers so an open dialogue on medication nonadherence can be initiated. This may be a first step in a right direction in improving medication adherence in patients undergoing dialysis. In addition, current adherence assessment practices could be improved by formalising and integrating these practices into hospital policies and procedures. For example, by integrating adherence checklists into treatment sheets for routine assessments. Although easier said than done, having a dedicated and trained healthcare professional to measure adherence, is another key initiative that may improve medication adherence among dialysis patients. Finally, the importance of frequent discussion with patients to identify concerns they may have related to their medications cannot be overestimated.

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STRUCTURE OF THE THESIS

This thesis initially describes the existing literature on medication adherence and gradually progresses towards study findings that investigate determinants of medication adherence, current practices and impediments to assessing adherence. Furthermore it considers, strategies to improve adherence assessment practices in routine dialysis care. The thesis concludes with a general discussion on issues surrounding assessment of medication adherence in patients undergoing dialysis, and recommending strategies on how to address and overcome these issues in future.

Chapter 1 provides a brief synopsis on medication adherence, primarily dealing with the general attributes of adherence in relation to chronic diseases such as: definition and terminology used; measurement methods; the magnitude of the problem; consequences and economic implications of nonadherence; determinants of adherence; and strategies used to improve poor adherence in patients with chronic diseases.

Chapter 2, is a systematic review summarising the existing literature on nonadherence and identifying factors associated with medication nonadherence in chronic kidney failure patients undergoing haemodialysis treatment. This chapter highlights the nonadherence prevalence pattern and a number of patient-related, disease-related, and medication-related factors contributing to medication nonadherence in patients undergoing haemodialysis.

Chapter 3, describes the findings of an exploratory study that investigated medication regimen complexity, perceived burden of medicines, and health-related quality of life, as potential predictors of adherence. Fifty-three adult (≥ 18 years) patients undergoing haemodialysis from the outpatient haemodialysis centre at the Royal Hobart Hospital (RHH), Hobart, Australia, participated in this study. The findings

of this exploratory study suggest that older patients with higher levels of comorbidities and highly complex regimen are more likely to be adherent based on an objective measure of assessment. This study emphasised that dialysis care professionals should be more vigilant towards supporting younger patients during their early adjustment to haemodialysis treatment.

Chapter 4, reports on findings from the qualitative study that explored determinants of medication adherence and examined the differential perspectives on medication-taking behaviour shown by adherent and nonadherent patients undergoing haemodialysis. Thirty patients, who had earlier participated in an exploratory study described in Chapter 3, completed this qualitative study. The qualitative themes generated comprised of patient-related (knowledge, awareness, attitude, self-efficacy, action control, and facilitation); health system/healthcare team-related (quality of interaction, and mistrust and collateral arrangements); therapy-related (physical characteristics of medicines, packaging, and side effects); condition-related (symptom severity); and social/economic factors (access to medicines, and relative affordability).

Chapters 5 and 6 describe the findings from a cross-sectional survey of renal healthcare professionals regarding their perceptions, current practices, and barriers to assessing medication adherence in patients undergoing dialysis. Chapter 5 particularly focuses on renal pharmacists' perceptions, whereas chapter 6 deals with the renal nurses' perceptions. A total of 113 renal nurses and 41 specialist renal pharmacists across Australia, participated in this study. The survey findings highlighted the fact that dialysis centres routinely rely on objective measure of adherence assessment, such as blood results, to detect nonadherence issues with little to no attention being paid to patient engagement via self-reported measures. Also, owing to the lack of dedicated healthcare professionals, the survey participants

emphasised on the importance of having a dedicated renal pharmacist in dialysis centres to facilitate assessment and promotion of medication adherence in patients undergoing dialysis treatment.

Chapter 7, describes the outcomes of the qualitative study conducted in renal healthcare professionals that identified perceived barriers to assessing adherence and strategies to improve adherence assessment practices in dialysis settings. Eighteen renal professionals, including 6 renal pharmacists and 12 renal nurses, who had earlier participated in the cross-sectional survey, described in Chapters 5 and 6, completed this qualitative study. A number of organisational-related, professional-related, and patient-related barriers to assessing adherence were identified. Similarly, participants proposed a variety of ways by which adherence assessment practices could be improved. These included: formalisation of assessment process; integration of assessment process and tools into routine; and using multidisciplinary support.

Chapter 8, discusses the findings from all the quantitative and qualitative studies reported in earlier chapters. It provides recommendations and future research directions related to adherence assessment practices designed to improve medication adherence in patients undergoing dialysis therapy. **Figure 1** illustrates the overall structure of this thesis.

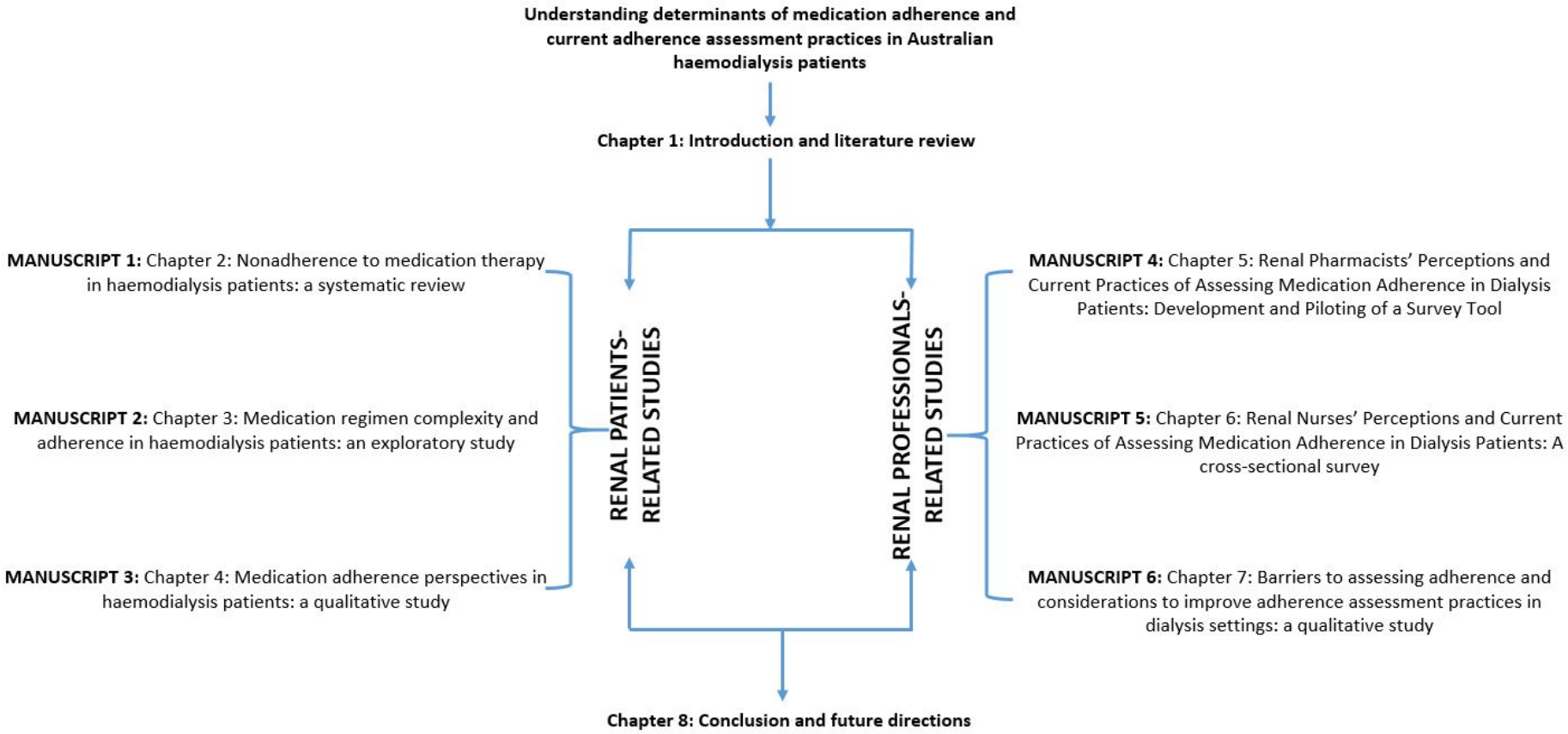

Figure 1. Structure of the thesis

CHAPTER ONE

1. INTRODUCTION

1.1. Background

"Keep a watch…on the faults of the patients, which often make them lie about the taking of things prescribed. For through not taking disagreeable drinks, purgative or other, they sometimes die."

- Hippocrates of Kos, Decorum

(460-370 BC)

After more than 2,000 years, the above admonitions from the "father of medicine" are still relevant. Over half the time patients with chronic conditions do not take their medicines as prescribed [1], and an estimated 125,000 Americans die each year due to nonadherence [2]. Due to increasingly complicated medication regimens for patients with chronic illness, the situation is likely to worsen, unless healthcare professionals strive to promote adherence with their patients [1].

Developing a new efficacious medication requires significant time, money and resources. An estimated $2.6 billion is spent on developing a new drug molecule for therapeutic use [2], whereas the avoidable annual opportunity cost lost due to adherence failure is around $105 billion [3]. Despite an increasingly echoed slogan of patient first, the practice of medicine is mainly focused on selecting the best treatment for their patients while placing a much lesser emphasis on engaging them to achieve optimum adherence to the selected regimen. It seems like the current clinical practices have become oblivious to the fine thread called "adherence" that lies between the

“treatment” and the “outcomes” [1]. Despite the fact that various direct and indirect methods have been routinely used to assess patient adherence, such as monitoring symptoms and clinical response of therapy, measuring biological markers, and, drug and metabolite levels in the blood [2], information generated from such assessments often ends up as ‘another observation’ in patients’ medical records. A standardised adherence assessment protocol that actually aims at recognising the medication-taking behaviour in patients with long-term therapy during their treatment process has been a missed opportunity in routine clinical settings. Effective regimens may be arbitrated as ineffective, dosage may be dangerously intensified, unnecessary diagnostic procedures may be ordered, and burden of healthcare cost may rise simply because of not recognising adherence as an issue during treatment process [4].

The former US surgeon general, Dr Charles E. Koop has plainly said, “drugs don’t work in patients who don’t take them” [2]. The profundity of this statement is a gentle reminder to the medical community that unless we monitor this fine thread of adherence as part of the treatment process, desirable outcomes may not always be achieved. Medication nonadherence in patients can lead to treatment failure, unnecessary additional treatments, exacerbation of disease, frequent hospitalisations, increased resource utilisation, patient frustration, increased morbidity, and, in rare cases, even death [1, 2, 5, 6]. Thus, medication adherence must receive greater attention in clinical practice, and should be considered a subject of exploratory and translational studies in order to mitigate or eliminate a major obstacle such as nonadherence to achieve better health outcomes.

Medication adherence becomes a challenging endeavour particularly in patients undergoing life-long therapies such as organ transplants, co-existing multiple comorbidities like diabetes and cardiovascular disorders, and end-stage kidney

disease (ESKD) patients undergoing dialysis [7]. In addition to their primary treatment regimen of dialysis, the ESKD patients often have multiple comorbidities such as diabetes, hypertension, anaemia, mineral and bone disorders, hyperlipidemia, and cardiovascular diseases [8]. Together with such comorbidities and complications associated with dialysis, ESKD patients require an average of 10-12 medications daily. Past findings suggests an overwhelmingly high median pill burden of 19 per day, with one quarter of dialysis patients exceeding 25 pills per day [9]. Increased pill burden is significantly associated with medication nonadherence in dialysis patients [9]. Compared to other chronic conditions like cardiovascular disease or HIV, nonadherence is highly prevalent in ESKD patients undergoing dialysis therapy [10], with nonadherence to phosphate binding medications alone ranging between 22.0% and 74.0% [11]. Suboptimal adherence in dialysis patients has led to increased morbidity and mortality, higher medication use, and repeat admissions leading to unwanted treatments, and higher cost burden [10]. Patients' medication-taking behaviour can be highly complex and individualistic in nature, and nonadherence as such might only be the tip of the iceberg with underlying multifaceted motives hidden behind. There is a gap in our understanding as to what factors contribute to medication nonadherence in ESKD patients undergoing dialysis and how adherence is measured during routine dialysis care. Understanding determinants of adherence in patients undergoing dialysis and the current practices of measuring adherence in dialysis settings may help in designing tailored interventions to resolve this significant issue.

1.2. Aims and Objectives

Aims

The overall aims of this research were to determine potential predictors of medication nonadherence in patients undergoing haemodialysis, explore current practices and barriers to assessing adherence, and identify strategies to improve adherence assessment practices in routine dialysis care.

Objectives

The specific research objectives were to:

- summarise existing literature on medication nonadherence and identify factors associated with medication nonadherence in patients undergoing haemodialysis;
- investigate prevalence patterns, socio-demographic, clinical and psychosocial factors contributing to medication nonadherence in Australian haemodialysis patients, and
- identify current practices of assessing medication adherence by the renal healthcare professionals, barriers to assessment, and strategies to improve adherence assessment practices in Australian dialysis centres.

1.3. Methodology

To achieve the research aims a number of related studies were conducted applying various study designs. For summarising the existing literature on medication nonadherence in patients undergoing haemodialysis, a systematic review approach was used. The conduct and reporting of this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline [12].

Following this, a mixed-method explanatory sequential design study [13] was used for achieving other specific research objectives. In explanatory sequential design, the quantitative data are collected first, which is then followed by the generation of qualitative data to help explain or elaborate on the findings from quantitative results. The rationale behind this approach is that the quantitative analysis offers a general understanding of the research problem, whereas the qualitative data enriches the research findings by exploring participants' perspectives in an in-depth manner [13].

Besides systematic review, this research was operationalised in two phases whereby in first phase a quantitative study of patients undergoing dialysis was conducted to determine predictors of adherence followed by the qualitative exploration of patients that identified socio-demographic, clinical and psychosocial factors associated with medication nonadherence. In the second phase of the research, renal healthcare professionals including renal nurses and pharmacists were surveyed to understand current practices of assessing medication adherence in patients undergoing dialysis. This was followed by qualitative investigation to identify barriers of measuring adherence and finding ways by which adherence measurement practices could be improve in dialysis settings (**Figure 2**).

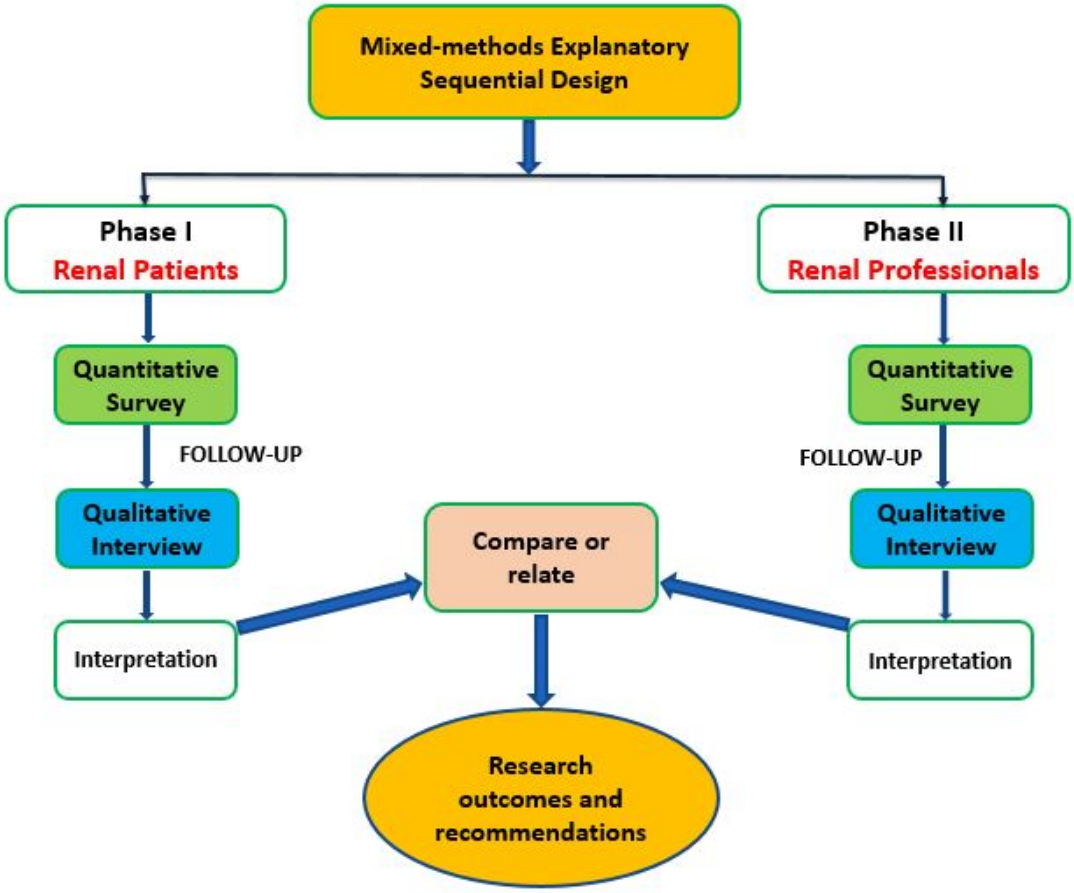

Figure 2. Research methodology

The conduct and reporting of quantitative survey followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline [14], whereas the COREQ (Consolidated Criteria for Reporting Qualitative Research) guideline was utilised during the conduct of qualitative research [15].

1.4. Literature Review

1.4.1. Terminologies Used to Define Adherence

Adherence to medication therapy, in general, is defined as the extent to which patients take their medications as prescribed by their healthcare providers [2]. The World Health Organisation (WHO) defines adherence to long-term therapy as “the extent to which a person’s behaviour taking medication, following a diet, and or executing lifestyle changes, corresponds with the agreed recommendations of a healthcare provider” [16, 17]. The terms “adherence”, “compliance”, and “concordance” are often used interchangeably. These enact different interpretations with respect to the healthcare provider-patient relationship, however.

The term “compliance” implies that a patient is passively following the prescriber’s instructions, and reflects a paternalistic attitude [1, 2, 6]. This has led to the term being criticised for its negative connotations of the patient-provider relationship. On the other hand, the term “concordance”, coined by the Royal Pharmaceutical Society of Great Britain in 1997 [18], intends to eliminate the implications of patient obedience by reaching a therapeutic alliance between a patient and a healthcare professional [19]. As healthcare services have adopted a more patient-focused approach to treatment, the term “adherence” is preferred by many healthcare professionals because it signifies that the treatment is based on a therapeutic alliance or an agreement established between patients and providers where the patient is playing an active role [2].

Medication adherence and nonadherence have been conceptualised in terms of either primary or secondary (non) adherence [20], or in terms of intentional and unintentional (non) adherence [17, 20, 21]. Primary nonadherence to medication refers to the act of never filling a prescription, whereas secondary nonadherence refers to

filling a prescription, but not taking the medication as prescribed [22]. The vast majority of the adherence research has focused on understanding secondary nonadherence behaviour in patients. In contrast, intentional nonadherence occurs when patients choose to ignore treatment recommendations by delaying, altering, or missing the dosage of their prescribed medicines [17, 23, 24]. Unintentional nonadherence, however, occurs due to a patient's lack of understanding, forgetfulness, or miscommunication with healthcare providers [17, 23, 25].

Vrijens et al. defined a new taxonomy of adherence by considering the process of medication-taking behaviour in patients [26]. The medication adherence process constitutes four different components: initiation, implementation, discontinuation, and persistence (**Figure 3**). *Initiation* is the start of the process, where patients take their first dose of the prescribed regimen. This is followed by *implementation,* which is the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen from initiation until the last dose taken by the patient. *Discontinuation* refers to the end of therapy, and is when the next dose to be taken is omitted or no more doses are taken afterwards. *Persistence* is the window between initiation and the last dose taken, and occurs immediately before discontinuation.

Based on this taxonomy, nonadherence can occur in different situations, such as late or non-initiation of the prescribed treatment, suboptimal implementation of the medication regimen, or early discontinuation of the treatment [26].

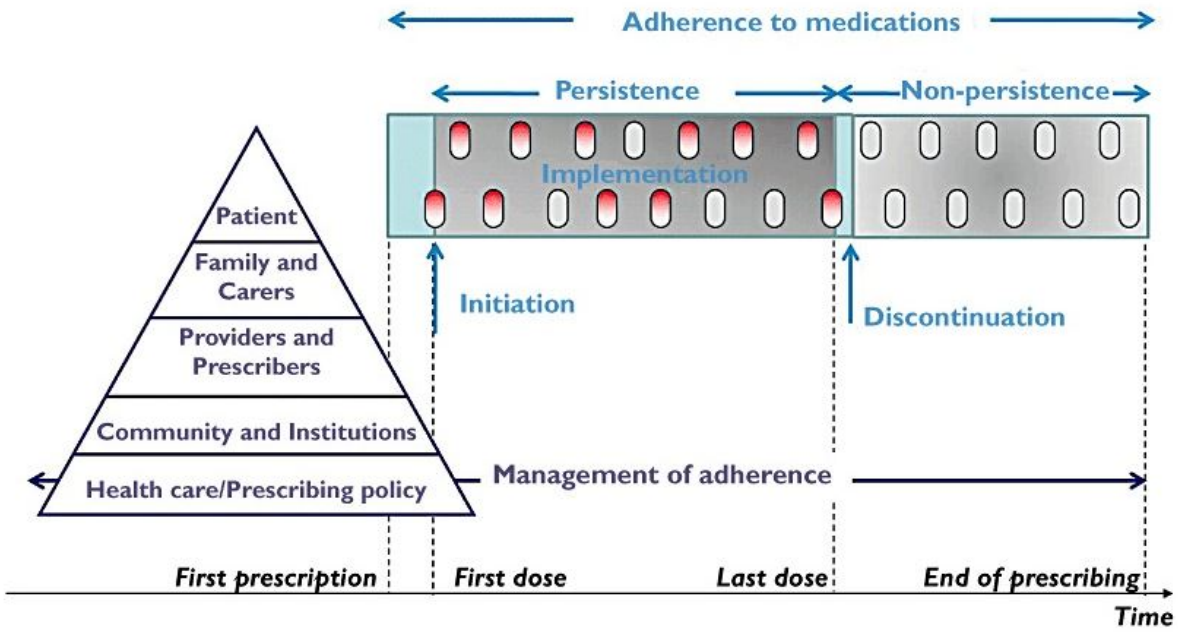

Figure 3. Illustration of the process of adherence to medications

(*Source: Vrijens et al. Br J Clin Pharmacol. 2012; 73(5): 691-705. Reproduced with permission from John Wiley and Sons, Inc.*)

1.4.2. Methods of Measuring Adherence

Measuring medication adherence is a challenging endeavour. Adherence outcomes may vary depending upon the methods used to assess adherence [11]. Although there is no "gold standard" method available for assessing adherence in clinical settings [2], a variety of approaches have been used that can be broadly classified into two types: objective and subjective measures [1, 23].

Objective measures can be either direct or indirect, as classified by Osterberg et al [2]. Direct methods comprise directly observed therapy, and the monitoring of blood levels for medicines, metabolites, or biological markers (Table 1). It should be noted, however, that variations in drug absorption and metabolism, a patient's tendency to hide drugs in their mouths and discard them, and the practicality of use in routine measurement, may limit the suitability of direct methods for assessing

adherence [27]. Nevertheless, use of direct methods is common in research related to high-risk medications, or when finances, invasiveness, and resource utilisation outweigh the public health demands to address global healthcare crises, such as tuberculosis treatment with DOTS (directly observed treatment, short-course) [28, 29]. Indirect objective methods comprise counting pills, measuring prescription refill rates, electronic monitoring, observing patients' clinical responses, and physical assessments [2]. Each of these methods have their own strengths and limitations regarding the measuring of medication adherence, as shown in Table 1, and their utilisation may depend upon data availability and the clinical setting involved.

Subjective measures of assessing adherence mainly involve asking patients, their families or caregivers, and health professionals about medication [1]. Subjective assessment can be performed either through patient interviews, or by using validated questionnaires [30]. In clinical settings, subjective measures are more popular among healthcare professionals as they provide real-time feedback, and are simple and economical to use [31]. Also, due to their practicality and flexibility, subjective measures are capable of identifying patient concerns related to their medication-taking behaviour, and can facilitate tailored interventions to resolve adherence issues [30].

Nevertheless, subjective adherence assessment is also prone to recall bias and social desirability responses, which involves reporting overly optimistic estimations of medication-taking behaviour by the patients to their healthcare professionals [27, 32]. As adherence measures differ in their definitions and assessment methods, using a combination of subjective and objective methods can be effective in detecting actual nonadherence behaviour in patients [33]. A summary of the methods of measuring medication adherence is depicted in **Table 1**.

Table 1. Methods of measuring medication adherence

Method	Advantages	Disadvantages
Objective measures		
Direct methods		
Direct observation of medication therapy	Most accurate	Routine use can be impractical
Measuring blood levels for medicine or metabolite	Objective	Expensive, may give false impression due to variations in metabolism and influenced by “white coat adherence”
Tracing biological marker in blood	Objective; placebos can be measured in clinical trials	Biological assays can be expensive and requires collection of bodily fluids
Indirect methods		
Pill counts	Objective, easy to implement and, quantifiable	Data alteration due to pill dumping, time consuming
Prescription refill	Objective and easy to obtain data	Ingestion of medicine cannot be guaranteed and requires closed pharmacy system for assessment
Electronic monitoring	Patterns of medication-taking behaviour can be easily tracked	Expensive and requires return visits for downloading medication vials data
Physical assessment (e.g., blood pressure, heart rate)	Easy to perform	Altered response due to poor absorption of drugs, increased metabolism, or lack of response
Clinical response of patient	Easy to perform	Clinical responses may be altered by other factors besides medicine
Subjective measures		

Method	Advantages	Disadvantages
Asking patients, family, caregiver, or professionals; use of validated questionnaires (e.g., MGLT-4, MMAS-8), and self-reports	Simple, inexpensive, and widely used in routine clinical practices	Susceptible for social desirability response and recall error due to time lag between clinic appointments
Patient diaries	Poor recall can be avoided	Patient can easily manipulate

Source: Osterberg and Blaschke. N Engl J Med 2005; 353:487-497. Abbreviations: MGLT, Morisky Green Levine Test; MMAS, Morisky Medication Adherence Scale

1.4.3. Magnitude of the Problem of Medication Nonadherence

According to the WHO, the incidence of medication adherence in chronic diseases in developed nations is estimated at only 50% [16]. The magnitude and consequence of suboptimal adherence in developing nations is projected to be much higher due to the limitation of health resources, and disparity in access to healthcare services [16]. Compared to acute illness, medication nonadherence rates in chronic conditions is remarkably higher [2], and persistence with long-term medications rapidly declines after the first few months of medication therapy [2, 34, 35], even if the patient has experienced a major cardiovascular event, such as a stroke (**Figure 4**).

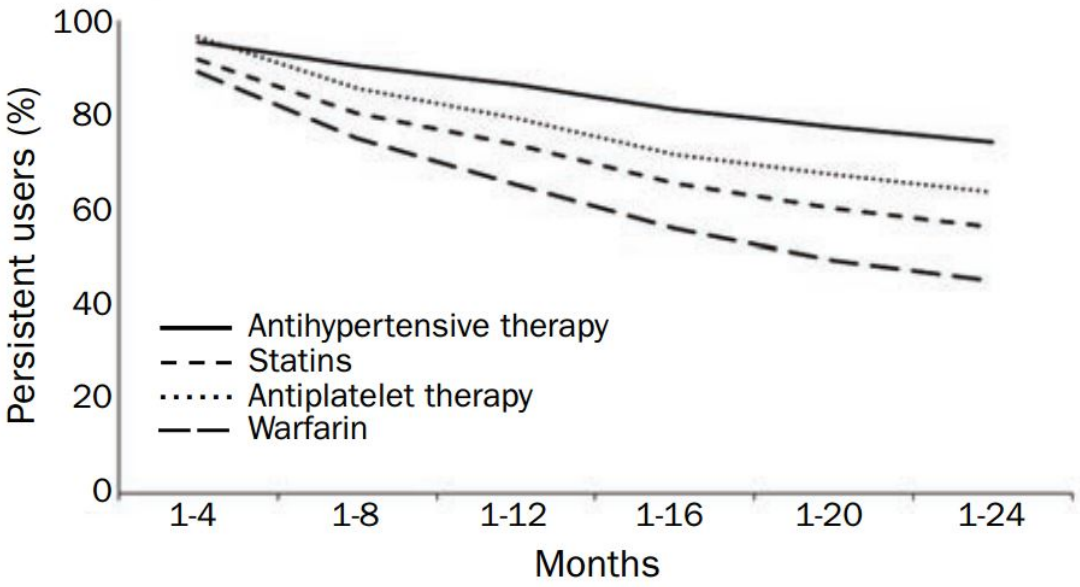

Figure 4. Persistence with secondary prevention medication over 24 months after ischemic stroke

(Source: Glader et al. Stroke. 2010;41(2):397-401. Reproduced with permission from Wolters Kluwer Health, Inc.)

The rate of medication nonadherence varies across populations, disease conditions, and the types of medications being assessed [27, 36]. The summary of nonadherence rates for different chronic conditions is illustrated in **Table 2**.

Table 2. Prevalence rates of medication nonadherence in chronic diseases

Conditions	Prevalence rates (%)	References
Respiratory		
Asthma	30.0 – 70.0%	[37, 38]
Chronic obstructive pulmonary disease (COPD)	60.0 – 90.0%	[39]
Musculoskeletal		
Osteoarthritis	33.0 – 44.0%	[40, 41]
Osteoporosis	30.0 – 60.0%	[42, 43]
Rheumatoid arthritis	20.0 – 70.0%	[44]
Mental disorders		
Schizophrenia	5.0 – 52.8%	[45]
Depression	13.0 – 55.7%	[46]
Gastrointestinal and metabolic disorders		
Diabetes Mellitus	6.9 – 61.5%	[47]
Inflammatory bowel disease (IBD)	43.0 – 72.0%	[48, 49]
Cardiovascular		
Heart failure	2.0 – 90.0%	[50]
Hypertension	43.0 – 65.5%	[51]
High cholesterol	8.0 – 82.0%	[52]
Infectious disease		
Tuberculosis	20.0 – 50.0%	[53, 54]
HIV/AIDS	55.0 – 77.0%	[55, 56]
Skin disease		
Psoriasis	33.4 – 78.4%	[57]
Genitourinary		
Chronic kidney disease (CKD)	22.0 – 74.0%	[11]
Patients on Haemodialysis	12.5 – 98.6%	[23]
Patients on Peritoneal dialysis	3.9 – 43.0%	[25]
Cancer		
Adults on oral antineoplastic agents	0.0 – 84.0%	[58, 59]

1.4.4. Consequences of Medication Nonadherence

Medication nonadherence can adversely affect the health outcomes of patients, leading to an increase in healthcare costs due to higher utilisation of medical resources,

unanticipated additional treatments, frequent hospitalisation, and emergency department visits. Nonadherence may also result in treatment failure, and ultimately the death of the patient. More than 10% of hospital admissions [60], and over 20% of preventable adverse drug events in elderly outpatients have been attributed to medication nonadherence [61]. Between 33% and 69% of all medication-related hospitalisation in the United States is linked with suboptimal adherence [2], incurring an annual healthcare expenditure of around $100 billion [2, 60].

Adherence failure has been associated with mortality in paediatric patients with asthma, with death rates up to five times higher in African-American children compared to their Caucasian counterparts [62, 63]. It may also result in drug resistance and re-emergence of highly contagious infections, such as tuberculosis, and cause serious threats to public health [64]. Similarly, nonadherence to antiretroviral therapy has been associated with increased viral load in patients with HIV/AIDS [65].

Another important aspect of nonadherence is the under-recognition of this issue, which can negatively influence medical decisions. For example, clinicians may attribute poor glycaemic control following nonadherence to therapeutic ineffectiveness, and increase the dosages of current medications or add new medications to the regimen. This may result in potentially adverse consequences, such as hypoglycaemia [66]. The consequences of medication nonadherence in chronic illnesses is summarised in **Table 3**.

Table 3. Complications resulting from medication nonadherence

Conditions	Consequences of nonadherence
Respiratory	
Asthma	Mortality in children [63]
COPD	Severe exacerbations, repeat admissions and emergency department visits [67]
Musculoskeletal	
Osteoporosis	Bone-related fractures [68]
Rheumatoid arthritis	Increased disease activity [69]
Mental disorders	
Schizophrenia	Relapse and repeat psychiatric admission [70, 71]
Depression	Emergence of depressive symptoms and medication inefficacy [72]
Gastrointestinal and metabolic disorders	
Diabetes	High blood pressure and altered lipid metabolism [73, 74], Stroke [27]
IBD	Systemic relapse and risk of colorectal cancer [75]
Cardiovascular	
High cholesterol	Acute myocardial infarction [76]
Hypertension	Acute myocardial infarction [76]
Congestive heart failure	Additional inpatient, outpatient, emergency room and pharmacy utilisation [77]
Infectious disease	
Tuberculosis	Drug resistance and disease re-emergence [64, 78]
HIV/AIDS	Higher viral load [79, 80]
Organ transplantation	Transplant failure [81, 82], decreased quality of life [83]

1.4.5. Economic Implications of Nonadherence

The true cost of nonadherence and its impact on health is often underestimated. The existing literature mainly examines the direct healthcare costs of nonadherence, which are often expressed as hospitalisation costs [84, 85] and hospital-related costs [86]. This does not consider the indirect costs of nonadherence, however, such as productivity and disability costs incurred by the patient and society [28]. The health-related indirect costs are estimated to be 2.3 times higher than the direct healthcare costs of nonadherence [87]. The relationship between nonadherence and associated healthcare costs is illustrated in **Figure 5**.

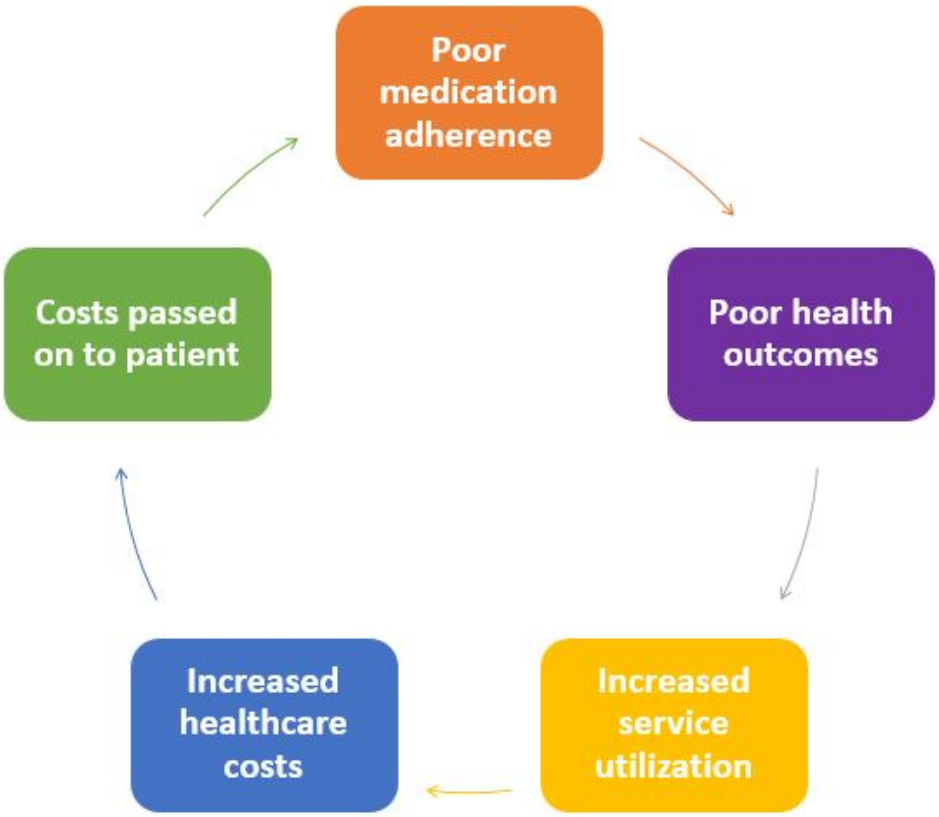

Figure 5. Relationship between nonadherence and associated healthcare costs

(*Source: Luga and McGuire. Risk Manag Health Policy. 2014; 7: 35-44. Reproduced with permission from Dove Medical Press)*

Suboptimal adherence to medication therapy results in poor health outcomes in patients, escalating healthcare service utilisation and overall healthcare costs. Although this may not be true for all healthcare systems, the increased expenditure is passed over to the patients through higher co-payments, or through higher costs to employers for coverage. With the increase in patient cost sharing beyond a threshold impedes medication adherence (**Figure 5**) [28]. The avoidable direct healthcare costs caused by medication nonadherence in the United States is estimated at $105 billion a year (**Figure 6**) [3].

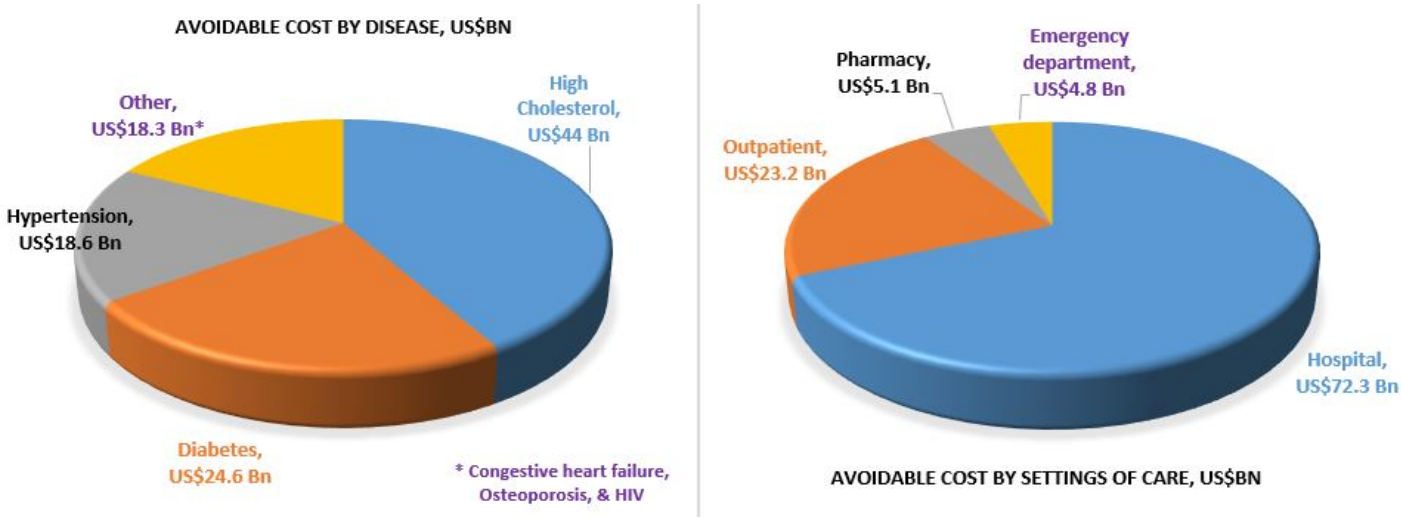

Figure 6. Avoidable cost of nonadherence to medication

(*Source: Avoidable Costs in U.S. Healthcare: The $200 Billion Opportunity from Using Medicines More Responsibly. Report by the IMS Institute for Healthcare Informatics. June 2013*)

The economic implications of nonadherence have been investigated in relation to various chronic illnesses, such as cardiovascular disease [27, 76, 88-91], respiratory [92-96], gastrointestinal and metabolic disorders [86, 97-101], infectious

diseases [102-104], psychiatric illnesses [105-107], and others [2, 5, 96, 108]. In a study conducted with congestive heart failure patients, the total healthcare costs reduced by 23% annually in adherent patients compared to nonadherent ones [88]. In another study looking at heart failure and myocardial infarction patients, adherence and persistence with angiotensin receptor blockers and angiotensin converting enzyme inhibitors resulted in a lower risk of repeat admission, and reduced healthcare costs [89].

A strong associations between healthcare costs and adherence to statin therapy has also been reported [90, 91]. In patients with chronic obstructive pulmonary disease (COPD), adherence as assessed using the proportion of days covered (PDC) was strongly associated with decreased emergency department visits and readmission, leading to a nearly 3% reduction in overall healthcare costs among the adherent patients [92]. Similarly, adherence to the maintenance medication therapy by COPD patients has been significantly associated with reduced Medicare expenditures, and a lower risk of repeat admissions [94].

Unlike COPD, patients with asthma only demonstrate improved healthcare costs if they are in high-risk cohorts with a history of repeat admissions [95, 96]. This suggests that cost savings may be achieved for patients with severe illnesses through adherence to their prescribed regimens [28, 95, 96]. In contrast, adherence to antiretroviral treatment in patients with HIV/AIDS has shown mixed results, with some studies reporting a positive correlation between adherence and decreased healthcare utilisation and associated costs [102], and some reporting no significant cost variances [103, 104].

Numerous studies have also been conducted to investigate the association between adherence and the cost of diabetes, with the vast majority showing cost reduction with increased adherence to antidiabetic medications [86, 97-101]. On the other hand, healthcare cost research looking at other chronic illness, such as depression, musculoskeletal conditions, neurologic disorders, and some gastrointestinal and metabolic diseases, has shown variable associations with adherence [2, 5, 96, 105-108].

1.4.6. Determinants of Poor Medication Adherence

Suboptimal adherence to medication therapy can severely compromise health outcomes in patients. Understanding the determinants of poor medication adherence can be helpful in designing tailored interventions to tackle nonadherence issues. An extensive body of literature has identified the determinants of poor adherence in chronic diseases, and these factors can be broadly summarised into patient-related, provider-related, and external factors [2, 28, 109], as shown in **Figure 7**.

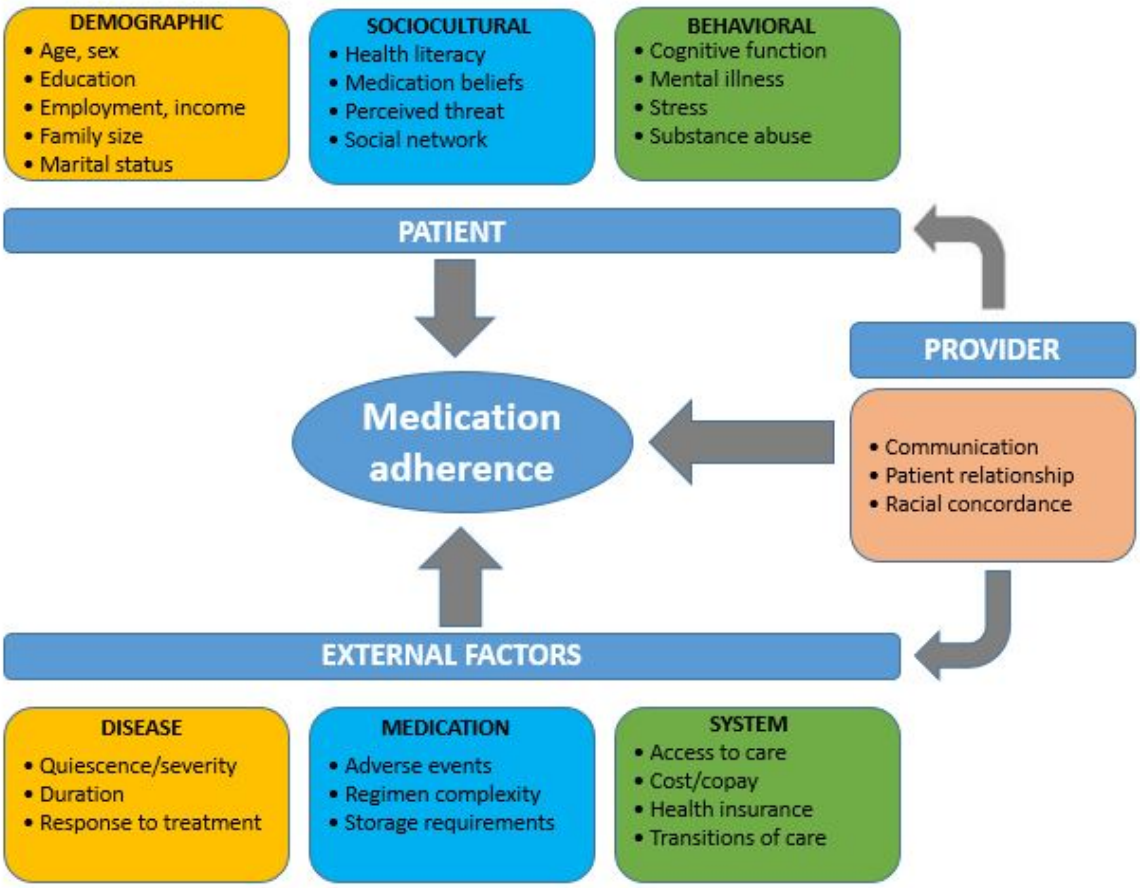

Figure 7. Selected determinants of medication adherence

(*Source: Luga and McGuire. Risk Manag Health Policy. 2014; 7: 35-44. Reproduced with permission from Dove Medical Press*)

The WHO has classified the determinants of medication adherence into five broad categories: patient-, condition-, therapy-, socioeconomic-, and health system-related factors [16, 27], as depicted in **Figure 8**. Medication adherence research has mainly focused on exploring patient-related dimensions, rather than on understanding other aspects of the healthcare system that may contribute to nonadherence behaviour in patients with chronic illnesses [110, 111]. The determinants of medication adherence in haemodialysis patients is discussed in detail in Chapters 3-5.

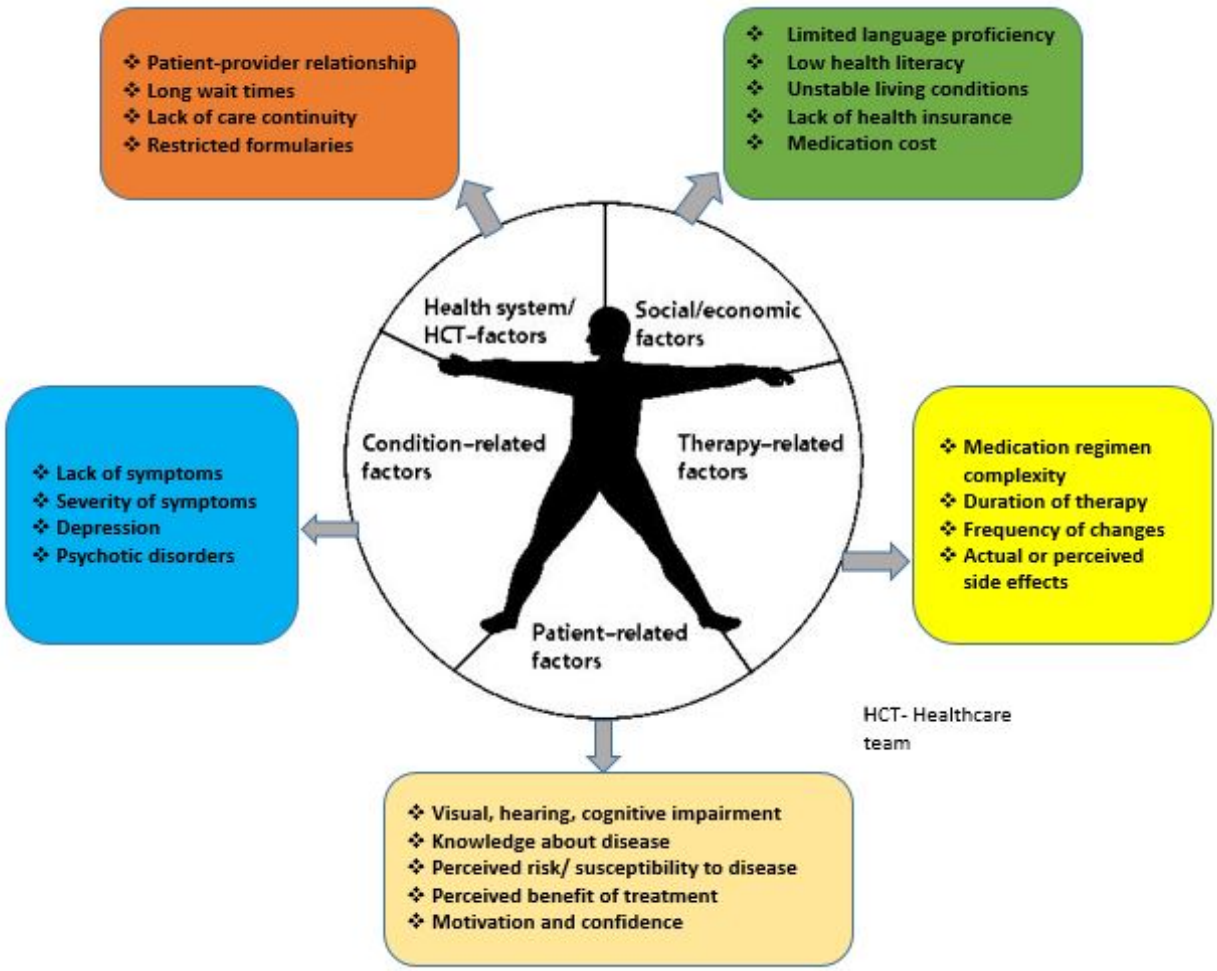

Figure 8. Five interacting dimensions affecting medication adherence

(*Source: Sabaté E. Adherence to long-term therapies- evidence for action. Geneva, Switzerland: World Health Organisation. 2003; NEJM Catalyst, catalyst.nejm.org © Massachusetts Medical Society*)

1.4.7. Strategies Used to Improve Poor Medication Adherence

Interventions to improve medication adherence have been more successful with patients with acute conditions compared to patients with chronic diseases. According to a Cochrane review, less than 45% of the interventions reported in 70 randomised controlled trials were actually associated with improved adherence with long-term therapies, and out of that only around 30% led to improved treatment outcomes [112]. This shortfall is mainly attributed to the focus of the interventions being unidimensional

and patient-centric [16]. The success of the intervention may depend on exploring and identifying the issues associated with all five of the WHO dimensions [16].

Demonceau et al. have classified the adherence intervention components into eight different types [113]: (1) *Treatment simplification,* which involves simplifying the dosage schedule (e.g. qd vs bid) or changing the dosage formulations (e.g. liquid to tablets). (2) *Cognitive–educational,* which presents information individually or in a group setting, and delivers it verbally, in written form, and/or audio-visually. This is designed to educate and motivate patients to make informed decisions about their therapy. (3) *Behavioural–counselling,* which shapes or reinforces behaviour, and empower patients towards self-management. (4) *Social–psycho-affective,* which focuses on providing psychosocial support to facilitate behaviour change. (5) *Electronically monitored adherence feedback,* which is designed to provide feedback on dosing histories through electronic medication-event monitoring. (6) *Technical reminders,* such as electronic and communication devices to remind patients to take their medicines. (7) *Technical equipment* for monitoring disease management, e.g. blood pressure measurements. (8) *Rewards* such as cash reinforcements, etc. A summary of the interventions used to improve medication adherence in patients with chronic diseases is presented in **Table 4**.

Table 4. Intervention used to improve medication adherence in chronic diseases

Condition	Intervention type	Description	Effect on clinical outcomes
Hypertension	Cognitive-educational	In-person and telephone follow-up educational sessions	Effective [114]
	Treatment simplification	Simplifying medication regimen, once daily vs twice daily	Ineffective [115]
	Treatment simplification, Cognitive-educational, and Use of technical equipment	Blood pressure monitoring at home, education on side-effects, and telephone follow-up	Effective [116]
High cholesterol	Cognitive-educational, Electronic monitoring-feedback, and Use of technical reminders	Providing information on disease, risk factors and dietary requirements, Electronic medication-event monitoring, and using beep-card reminder	Not Available [117]
Heart failure	Cognitive-educational, and Behavioural counselling	Providing education and written instructions on medication use	Ineffective [118]
	Treatment simplification	Simplifying medication regimen, once daily vs twice daily	Ineffective [119]
Diabetes	Cognitive-educational, and Behavioural counselling	4- weeks in-person and telephone follow-up educational sessions	Effective [120]
	Treatment simplification	Simplifying medication regimen, once daily vs twice daily	Effective [121]
Asthma	Rewards	Metered dose inhaler spacer with incentive toy in paediatrics	Ineffective [122]

Condition	Intervention type	Description	Effect on clinical outcomes
	Behavioural counselling	Providing written action plan for asthma attack and discharge instructions after acute-care visit	Effective [123]
HIV/AIDS	Behavioural counselling, Social-psycho-affective intervention, and Technical reminder use	Peer support, scheduled social gatherings, telephone calls to participants by their peers, and pager support	Ineffective [124]
	Cognitive-educational, Behavioural counselling, and Electronic monitoring-feedback	Providing tailored adherence information, goal setting, feedback on adherence to estimate progress towards goal, self-monitoring	Effective [125]
	Treatment simplification	Simplifying medication regimen, once daily vs twice daily	Ineffective [126]
Depression	Cognitive-educational, and Behavioural counselling	Coaching sessions and adherence promotional videos	Ineffective [127]
	Behavioural counselling, and Electronic monitoring-feedback	Counselling support and electronic monitoring-feedback	Ineffective [128]
Osteoporosis	Behavioural counselling, and Technical equipment	Interviewing, nurse monitoring, and monitoring biological marker and feedback	Not Available [129]
	Behavioural counselling, and Technical equipment	Monitoring biological marker and feedback, and counselling on reminders by linking patient's daily habits with taking medicines	Not Available [130]
Kidney transplantation	Treatment simplification	Simplifying medication regimen, once daily vs twice daily	Effective [131]

1.4.8. Medication Nonadherence in Chronic Kidney Disease

Chronic Kidney Disease (CKD) is defined by the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) as the presence of kidney damage or decreased kidney function (an estimated glomerular filtration rate, eGFR, of <60 mL/min per 1.73 m^2) for a period of three months or more [132]. Whereas end-stage kidney disease (ESKD) is characterised by chronic kidney failure with eGFR <15 mL/min per 1.73 m^2, necessitating renal replacement therapy (RRT) in the form of either dialysis or transplantation. CKD often co-exists with other chronic conditions, such as diabetes and hypertension, and CKD patients prior to undergoing RRT have a daily pill burden of 6-8 medications. If the disease progresses into ESKD, however, the average pill burden increases to 12 medications per day [133].

As anticipated, high pill burden imposes increased personal and financial burdens on patients, leading to an inevitable problem of medication nonadherence. An estimated 26-28% of patients with CKD who are not on dialysis are nonadherent to their medication therapy [134]. The rate of nonadherence is overwhelmingly high in ESKD patients undergoing dialysis treatment, and ranges between 22% and 74% (with an average of 51%) [11]. Poor medication adherence in patients with CKD has led to uncontrolled hypertension, disease progression into dialysis, increased medication use, and repeat admissions leading to unwanted treatment and increased financial burden [8]. The detrimental effects of medication nonadherence in CKD is of grave concern as it can negatively impact the quality of patients' lives. It is imperative that healthcare professionals remain aware of the factors contributing to medication nonadherence behaviour, particularly in patients taking long-term medications, e.g. CKD and ESKD patients undergoing dialysis treatment. Chapter 2 discusses the issues surrounding medication nonadherence in patients undergoing haemodialysis in detail.

CHAPTER TWO

2. NONADHERENCE TO MEDICATION THERAPY IN HAEMODIALYSIS PATIENTS: A SYSTEMATIC REVIEW

2.1. Abstract

Background: Patients with end-stage kidney disease (ESKD) are often prescribed multiple medications. Together with a demanding weekly schedule of dialysis sessions, an increased number of medicines and associated regimen complexity, these patients are predisposed to a high risk of medication nonadherence. This review summarises existing literature on nonadherence and identifies factors associated with nonadherence to medication therapy in patients undergoing haemodialysis.

Methods: A comprehensive search of PubMed, Embase, CINAHL, PsycInfo, and the Cochrane Database of Systematic Reviews covering the period from 1970 through to November 2014 was performed, following pre-defined inclusion and exclusion criteria. Reference lists from relevant materials were reviewed. Data on study characteristics, measures of nonadherence, prevalence rates and factors associated with nonadherence were collected. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines was followed in conducting this systematic review.

Results: Of 920 relevant publications, 44 were included. The prevalence of medication nonadherence varied from 12.5% to 98.6%, with widespread heterogeneity in measures and definitions employed. Most common patient-related factors significantly associated with nonadherence were a younger age, non-Caucasian

ethnicity, illness interfering with family life, being a smoker, and being single, divorced or widowed. Similarly, disease-related factors include longevity of haemodialysis, recurrent hospitalisation, depressive symptoms and having concomitant illness like diabetes and hypertension. Medication-related factors such as the daily tablet count, the total pill burden, the number of phosphate binders prescribed and the complexity of the medication regimen were also associated with poor adherence.

Conclusions: A number of patient-, disease-, and medication-related factors are associated with medication nonadherence in patients undergoing haemodialysis. Clinicians should be aware of such factors so that adherence to medications can be optimised in patients undergoing haemodialysis. Future research should be directed towards well-designed prospective longitudinal studies developing standard definitions and validating available measurement tools, while focusing on the role of additional factors, such as psychosocial and behavioural factors, in predicting nonadherence to medications.

Keywords: Adherence; end-stage kidney disease; haemodialysis; medication regimen complexity

2.2 Introduction

End-stage kidney disease (ESKD) is one of the leading causes of mortality with over one million people dying worldwide every year [135]. The incidence of ESKD is increasing globally, at an estimated annual rate of 7% [136]. Despite recent advances in the management of ESKD, the cardiovascular and non-cardiovascular mortality risk in patients undergoing haemodialysis is eight times greater than for people in the general population [137, 138].

The progression of chronic kidney disease to ESKD is often associated with additional comorbidities such as diabetes and cardiovascular diseases [8]. Patients with ESKD are at high risk of developing imbalances in calcium and phosphate haemostasis, anaemia, hyperlipidaemia, and secondary hyperparathyroidism [139]. Consequently, patients on haemodialysis often require an average of 10-12 regular medications including, but not limited to, phosphate binders, vitamin D preparations, calcimimetics, antihypertensives, antidiabetics, erythropoiesis-stimulating agents and iron supplements [140, 141]. The resultant complexity of the medication regimen in patients with ESKD predisposes them to a high risk of adverse drug events and subsequent nonadherence [140].

Medication nonadherence can be intentional or unintentional. Intentional nonadherence may occur when patients choose to ignore treatment recommendations by delaying, altering or missing the dosage of prescribed medicines [24]. Unintentional nonadherence, on the other hand, is due to a patient's lack of understanding, forgetfulness or miscommunication with healthcare providers [25]. Regardless of being intentional or unintentional, medication nonadherence prevents patients from gaining the full benefit of the prescribed medications. Furthermore, medication nonadherence in patients with ESKD has been associated with increased mortality

and hospitalisations [142, 143]. Thus, adherence to medication therapy is a key component of the effective management of patients with ESKD [142-145].

To date, there are few review articles addressing specific issues on identifying predictors and determinants of nonadherence to medication therapy in patients undergoing haemodialysis [6, 10, 11, 146, 147]. Existing literature is limited to non-systematic reviews examining nonadherence to dialysis treatment as a whole by including medication, dialysis attendance, and diet and fluid restrictions [17, 143, 148, 149]. It has been observed that about 50% of patients with chronic conditions are nonadherent to medication therapy [150], and the estimates of nonadherence to oral medications in patients undergoing haemodialysis ranged from 3 to 80% [147]. A review that specifically focussed on phosphate binder medication in patients undergoing haemodialysis reported rates of nonadherence ranging between 22 and 74% [11]. This wide variation in the reported rates of nonadherence was attributed partly due to the heterogeneity of definition and the methodology of assessing nonadherence in the studies.

The aims of this systematic review were:

1. to identify various methods used to assess nonadherence in patients undergoing haemodialysis;
2. to summarise current literature on nonadherence and estimate the prevalence of medication nonadherence in patients undergoing haemodialysis, and
3. to describe patient-, disease-, and medication-related factors associated with nonadherence in patients undergoing haemodialysis.

2.3. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed in conducting this systematic review [12]. The PRISMA checklist is supplied as **Appendix 1**.

2.3.1. Data Source and Search Strategy

We searched PubMed, Embase, CINAHL, PsycInfo, and Cochrane databases covering the period from 1970 through to November 2014. Search terms included combinations of Medical Subject Heading (MeSH) terms and keywords like “dialysis/haemodialysis”, “renal replacement therapy”, “end-stage renal disease”, “chronic renal failure”, “adherence/nonadherence”, “compliance/non-compliance”, “drug/medication”, and “regimen/schedule.” Details of the initial search strategy are provided in **Appendix 2**. A manual search of the references cited in each publication identified from the database search was conducted to identify additional relevant articles.

2.3.2. Study Selection

Titles and abstracts of the articles were screened to include relevant studies. In cases of insufficient information being ascertained from the title or abstract of a paper, a full copy of the article was obtained and screened to determine eligibility. Each article was evaluated for inclusion by two reviewers (SG and RLC) and disagreements between the reviewers were resolved by discussion with the third reviewer (STRZ).

Studies were included in this review if they fulfilled all of the following criteria: articles published in peer-reviewed journals, studies conducted in patient ≥ 18 years, undergoing haemodialysis treatment that included measure(s) of adherence or nonadherence related to medication therapy, and provided numeric results on rates of adherence or nonadherence. All adherence measures such as self-reporting, physician/nurse estimations, pill counts, prescription refills, and electronic monitoring were considered if a definition of nonadherence were provided, and nonadherence rates were reported. Studies with a longitudinal or cross-sectional design were included for review. Interventional studies were considered if baseline rates were provided. The publication language was not restricted to English only. Studies were excluded if they reported only adherence outcomes to non-medication interventions such as dialysis exchanges, diet or fluid restrictions, and exercise, if they did not clearly define or report rates of nonadherence, or if they were reviews, protocols, editorials, letters or dissertations (**Figure 9**).

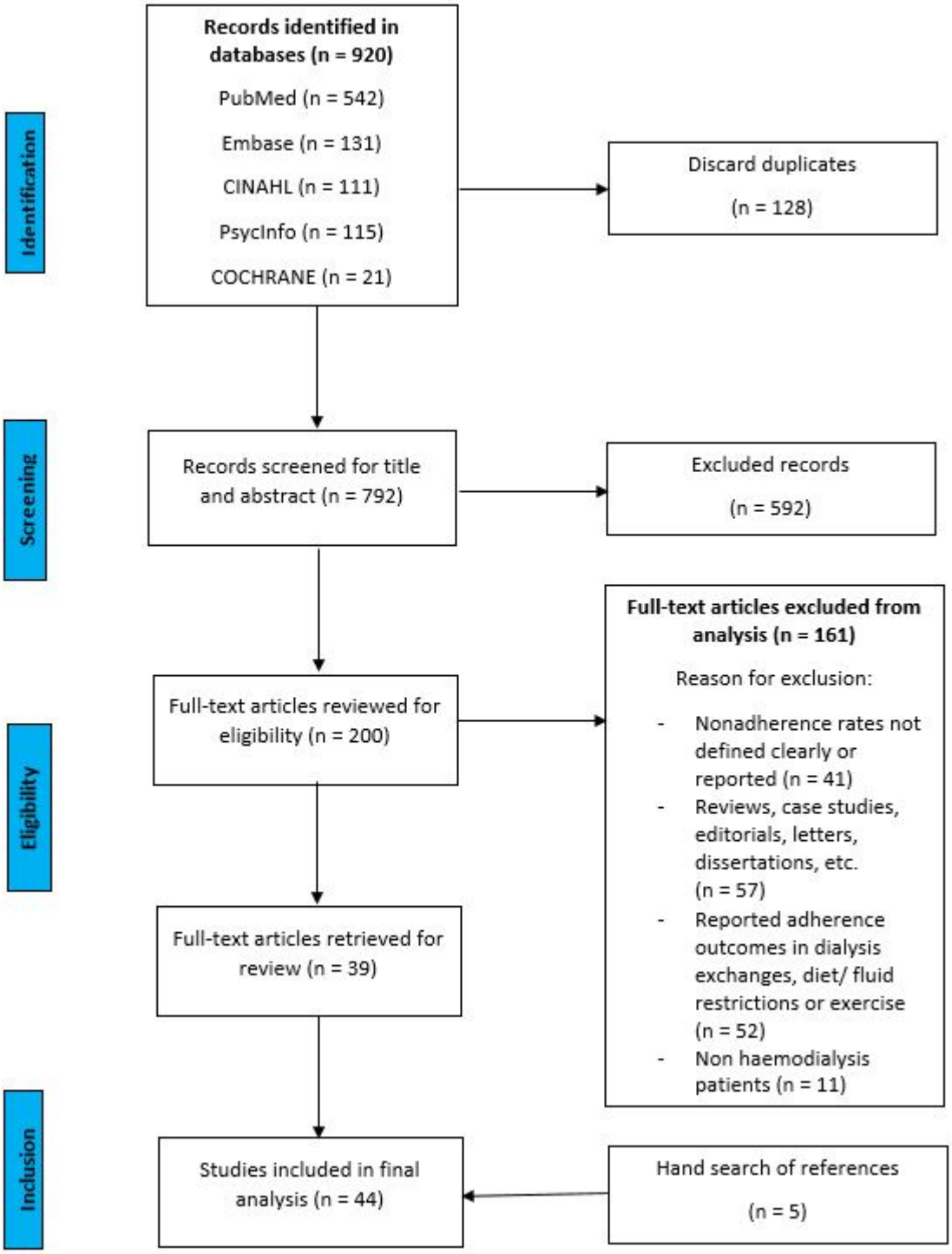

Figure 9. Flowchart of study selection for systematic review

2.3.3. Data Extraction and Analysis

Data from the included studies were extracted by one reviewer (SG) followed by verification of all data against the original studies by the second reviewer (RLC). Information extracted included: author, year of publication, country of origin, study design (prospective, retrospective, cross-sectional, and so on), participant characteristics, number of patients, age, gender, types of medications, adherence assessment method, definition of nonadherence, rates of nonadherence, and factors reported as being associated with nonadherence.

Data analysis involved a descriptive summary of included studies. More effective synthesis of results such as meta-analysis was not considered due to inconsistent reporting of results and variation in the type of statistical analyses performed. Several methods of assessing nonadherence were utilised. We grouped these methods into three broad categories: (1) objective/ direct measures, such as pill count, prescription refill or using medication event monitoring devices; (2) subjective/ indirect measures that are based on patients' self-reports or assessment by healthcare professionals and (3) biochemical measures that included measuring of pre-dialysis serum phosphate levels (SPL). To achieve our first objective, we performed frequency counts of each of the methods used to assess nonadherence. To attain the second objective, we grouped reported prevalence of medication nonadherence according to the three overarching subgroup measures and findings were collated using a summary bar chart. Our third objective was satisfied by extracting factors associated with nonadherence and presenting them in a tabular format, according to statistically significant and non-significant findings across studies per explanatory variables. This method was employed due to inconsistent reporting and unpredictable heterogeneity of the statistical analysis performed in the primary studies.

2.3.4. Quality Assessment

Quality assessment of included studies was independently carried out by two reviewers (SG and RLC) using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies [151]. This tool addresses six quality components: selection bias, study design, confounders, blinding, data collection methods, and withdrawals and dropouts. Sections on confounders and blinding were deleted in our adapted version as they were considered irrelevant to this review [25]. The components are rated as strong, moderate or weak according to a standardised guide and dictionary set for the instrument. Any discrepancies were resolved by discussion with the third reviewer (STRZ).

2.4. Results

2.4.1. Description of Included Studies

A flow diagram of the literature search and identification of relevant articles for review is depicted in **Figure 9**. Overall, 920 potentially relevant articles were identified. In total, 44 articles are summarised and evaluated in this systematic review. **Table 5** shows the characteristics of included studies.

Half (n = 22) of the studies [9, 145, 152-171] were conducted in North America, 15 were carried out in Europe [33, 150, 172-184], four were conducted in Asia [185-188], and two studies were performed in South America [189, 190]. One included study had a multi-centre site and was conducted in ten different countries [191].

Most of the included studies (n = 32) were cross-sectional in design [9, 33, 158-161, 163-166, 168-175, 177, 178, 180-191], with another seven having a prospective

nature [150, 154, 157, 162, 167, 176, 179], and five having a retrospective study design [145, 152, 153, 155, 156].

The sample size varied greatly from a minimum of 19 participants [171] to a maximum of 11,732 participants [152]. Overall, half (n = 22) of the included studies had a sample size of more than 100 participants [9, 33, 145, 150, 152, 155, 160, 162, 163, 166, 170, 172-174, 176, 178, 181, 182, 185, 187, 190, 191]. Moreover, five studies had more than 1000 participants each [145, 152, 155, 166, 191]. All included studies were comprised of patients with ESKD, receiving treatment at hospital-based outpatient haemodialysis centres.

Table 5. Characteristics of studies included in systematic review

Author, Year	Country	Patients (% Male)	Age (Years), Mean ± SD or Range	Medication	Assessment Method	Nonadherence (NAD) to Medication		Design (Study quality[a])
						Definition	Rates, n (%)	
Nonadherence based on patient self-reports								
Alkatheri et al., 2014	Saudi Arabia	89 (52.8)	15.0 – 65.0	PB	Self-report (MMAS-8)	Score < 7 classified as NAD	64 (71.9)	CS (M)
Ossareh et al., 2014	Iran	150 (47.3)	46.5 ± 16.4	PB [$CaCO_3$ (n = 136), $Al(OH)_3$ (n = 29), SA (n = 26)]	Self-report (SMAQ) Self-report (DIPQ)	Responding to any of the question with a NAD answer Taking < 66% of prescribed medication	37 (24.7) $CaCO_3$, 66 (48.5) $Al(OH)_3$,26 (89.7) SA, 11 (42.3)	CS (M)
Chater et al., 2014	UK	221 (52.0)	58.1 ± 14.2	PB [$CaCO_3$, $Al(OH)_3$, SA, $Ca(C_2H_3O_2)_2$]	Self-report (7-item MARS)	Score ≤ 28 classified as low adherers	68 (30.8)	CS (M)
Arenas et al., 2013	Spain	181 (56.9)	59.9 (21-86)	PB [$CaCO_3$, $Al(OH)_3$, $Ca(C_2H_3O_2)_2$ SA, LC], CM, Vitamin D	Self-report (SMAQ)	Responding to any of the question with a NAD answer	110 (60.8) (at baseline visit) 79 (71.8) (at 6 month)	P (M)

Author, Year	Country	Patients (% Male)	Age (Years), Mean ± SD or Range	Medication	Assessment Method	Nonadherence (NAD) to Medication		Design (Study quality[a])
						Definition	Rates, n (%)	
Santana & Diaz, 2013	Spain	106 (71.0)	61.0 ± 13.0	PB [$CaCO_3$, $Al(OH)_3$, SA, $Ca(C_2H_3O_2)_2$], CM (Cinacalcet)	Self-report (SMAQ)	Responding to any of the question with a NAD answer	40 (37.7)	CS (M)
Theofilou, 2013	Greece	168 (62.5)	62.0	NA	Self-report (5-item MARS)	Score < 20 classified as low adherers	42 (25.0)	CS (M)
Martins et al., 2013	Brazil	502 (66.3)	47.0 ± 13.3	PB	Interview	Reporting missed dose	330 (65.7)	CS (M)
Garcia-Llana et al., 2013	Spain	30 (60.0)[b]	60.6 ± 16.7	AHT (n = 17) PB (n = 25)	Self-report (MGLT-4)	Responding to any of the question with a NAD answer	AHT, 15 (90.9) PB, 17 (68.4)	CS (M)
Rosenthal Asher et al., 2012	USA	85 (40.0)[b]	55.9 ± 13.2	NA	Self-report (ITAS-M)	Score ≤ 9 classified as low adherers	11 (13.0)	P (M)
Wileman et al., 2011	UK	76 (60.5)	63.1 ± 15.4	PB	Self-report (MAQ)	Responding to any of the question with a NAD answer	11 (14.5)	CS (M)
Neri et al., 2011	Italy	1,238 (-)	61.7 ± 14.5	NA	Self-report (MGLT-4)	Responding to any of the question with a NAD answer	644 (52.0)	P (M)

Author, Year	Country	Patients (% Male)	Age (Years), Mean ± SD or Range	Medication	Assessment Method	Nonadherence (NAD) to Medication		Design (Study quality[a])
						Definition	Rates, n (%)	
Cukor et al., 2009	USA	65 (46.0)[b]	51.1 ± 13.0	NA	Self-report (ITAS-M)	Score ≤ 9 classified as low adherers	24 (37.0)	P (M)
Garcia et al., 2008	Spain	47 (63.0)[b]	70.0 ± 14.5	PB	Self-report (MGLT-4)	Responding to any of the question with a NAD answer	24 (52.3)	CS (M)
Hirth et al., 2008	Multinational[c]	7,852 (-)	62.4 ± 14.6	AHT, PB, CM	Self-report	Reporting cost related medication non-purchase	1052 (13.4)	CS (M)
Lindberg et al., 2007	Sweden	150 (60.0)[b]	63.6 ± 14.3	AHT, PB, CM, HDS	Self-report	Differences in the self-reported drug and prescription record	120 (80.4)	CS (W)
Holley & DeVore, 2006	USA	39 (44.0)[b]	67% over 50	NA	Self-report	Missing prescription filling, Reporting missed dose	11 (22.0) 21 (39.0)	CS (W)
Rahman & Griffin, 2004	USA	270 (53.0)	60.4 ± 16.0	AHT (n = 205)	Self-report	Reporting missed dose	47 (23.0)	CS (M)
Horne et al., 2001	UK	47 (48.9)	49.0 ± 17.3	NA	Self-report (BMQ)	Responding to any of the question with a NAD answer	27 (57.4)	CS (M)

Author, Year	Country	Patients (% Male)	Age (Years), Mean ± SD or Range	Medication	Assessment Method	Nonadherence (NAD) to Medication		Design (Study quality[a])
						Definition	Rates, n (%)	
Caraballo Nazario et al., 2001	USA	53 (41.7)	51.5 ± 14.3	AHT, PB	Structured Interview	Reporting missed dose	39 (75.0)	CS (M)
Gago et al., 2000	Spain	121 (56.2)	62.8 ± 12.6	AHT (n = 49) PB [$CaCO_3$ (n = 104) $Al(OH)_3$ (n = 39)]	Self-report	Differences in the self-reported drug and prescription record	AHT, 6 (12.5) $CaCO_3$, 14 (14.0) $Al(OH)_3$, 4 (12.5)	CS (W)
Kaplan et al., 1994	USA	30 (40.0)	40.5 (14 – 69)	AHT, PB	Self-report	Reporting missed dose	20 (66.7)	CS (M)
Blanchard et al., 1990	USA	40 (50.0)	50.4 ± 16.4	Ca Supplements, PB, Vitamins	Self-report	Reporting missed dose	11 (27.5)	P (M)
Nonadherence based on objective measures								
Park et al., 2014	USA	11,732 (56.2)	69.4 ± 12.7	AHG (n = 3,819) AHT (n = 9,863) AL (n = 4,607) CM (n= 2,436)	MPR	MPR < 80% (Poor adherence)	AHG: 2,338 (61.2) AHT: 4,098 (41.5) AL: 2,118 (46.0) CM: 1,587 (65.1)	R (M)

Author, Year	Country	Patients (% Male)	Age (Years), Mean ± SD or Range	Medication	Assessment Method	Nonadherence (NAD) to Medication		Design (Study quality[a])
						Definition	Rates, n (%)	
				PB (n = 7,753)			PB: 6,068 (78.3)	
Porter 2013	USA	96 (53.1)	52.5 ± 14.6	PB (SA), CM, Vitamin D	Refill per EMR	Medication course either not started or partially completed	35 (36.5)	R (M)
Lee at al., 2011	USA	4,923 (53.3)	61.8 ± 13.8	CM (Cinacalcet)	MPR	≥ 180 days refill gap, MPR < 80% (Poor adherence)	2,247 (45.6) 1,304 (26.5)	R (M)
Gincherman et al., 2010	USA	79 (43.0)	51.0 ± 13.0	CM (Cinacalcet)	MPR	MPR < 80% (Poor adherence)	56 (70.9)	R (M)
Chiu et al., 2009	USA	233 (58.0)	52.9 ± 14.7	PB [$CaCO_3$, $Al(OH)_3$, $Ca(C_2H_3O_2)_2$, SA, LC]	Pill count	Taking < 80% of prescribed pills	144 (62.0)	CS (M)
Curtin et al., 1997	USA	135 (47.0)	63.2 ± 13.8	AHT (n = 83) PB (n = 98)	MEMS	Instance of bottle opening	AHT, 77 (92.8) PB, 96 (97.9)	P (M)
Nonadherence based on biochemical measures								
Wileman et al., 2015	UK	112 (61.6)	60.5 ± 16.9	PB	SPL	SPL > 5.0 mg/dL	79 (70.5)	CS (M)

Author, Year	Country	Patients (% Male)	Age (Years), Mean ± SD or Range	Medication	Assessment Method	Nonadherence (NAD) to Medication		Design (Study quality[a])
						Definition	Rates, n (%)	
O'Connor et al., 2008	UK	73 (60.3)	51.9 ± 14.7	PB	SPL	SPL ≥ 5.5 mg/dL	40 (55.0)	P (M)
Tijerina, 2006	USA	26 (0.0)	30 – 56	PB	SPL	SPL > 6.0 mg/dL	16 (61.5)	CS (M)
Saounatsou, 1999	Greece	60 (53.3)	49.4	PB	SPL	SPL > 5.0 mg/dL	17 (28.3)	CS (M)
Leggat et al., 1998	USA	6,251 (49.7)	57.8 ± 15.5	PB	SPL	SPL > 7.5 mg/dL	1,383 (22.1)	R (M)
Bame et al., 1993	USA	1229 (47.1)	56.7 (18 – 90)	PB	SPL	SPL > 6.0 mg/dL	612 (49.8)	CS (M)
Weed-Collins & Hogan, 1989	USA	30 (43.0)	25 – 80	PB	SPL	SPL > 5.5 mg/dL	19 (64.0)	CS (M)
Betts & Crotty, 1988	USA	46 (33.0)	41 - 60	PB	SPL	SPL > 5.0 mg/dL	35 (76.1)	CS (M)
Cummings et al., 1982	USA	116 (54.0)	54.8 (21 – 76)	PB	SPL	SPL > 5.5 mg/dL	81 (70.0)	CS (M)

Author, Year	Country	Patients (% Male)	Age (Years), Mean ± SD or Range	Medication	Assessment Method	Nonadherence (NAD) to Medication		Design (Study quality[a])
						Definition	Rates, n (%)	
Wenerowicz et al., 1978	USA	19 (68.4)	36.0 (19 – 70)	PB	SPL	SPL > 4.5 mg/dL	13 (68.4)	CS (M)
Nonadherence based on multiple measures								
Sgnaolin et al., 2012	Brazil	65 (49.2)	59.1 ± 14.7	AHT, PB	SPL	SPL > 5.5 mg/dL	25 (38.5)	CS (M)
					Self-report (MGLT-4)	Responding to any of the question with a NAD answer	36 (55.4)	
Chan et al., 2012	Malaysia	188 (48.9)	58.2 ± 10.5	PB	SPL	SPL > 5.0 mg/dL	63 (33.5)	CS (M)
					Self-report (DDFQ)	Score ≤ 3 classified as low adherers	93 (49.5)	
Arenas et al., 2010	Spain	165 (63.0)	65.2 ± 14.7	PB [$Al(OH)_3$, $Ca(C_2H_3O_2)_2$, SA]	SPL	SPL > 5.5 mg/dL	23 (13.9)	CS (M)
					Self-report (SMAQ)	Responding to any of the question with a NAD answer	66 (40.0)	

Author, Year	Country	Patients (% Male)	Age (Years), Mean ± SD or Range	Medication	Assessment Method	Nonadherence (NAD) to Medication		Design (Study quality[a])
						Definition	Rates, n (%)	
Lin & Liang, 1997	China	86 (-)	55.0 (45.0)	PB	MCA	SPL > 5.0 mg/dL	52 (61.0)	CS (M)
						Nurse assessment	26 (30.8)	
						Self-report	20 (23.6)	
Cleary et al., 1995	USA	51 (45.1)[b]	51.0 ± 17.0	AHT, PB, Vitamin D	SPL	SPL > 4.5 mg/dL	23 (45.1)	CS (M)
					Structured Interview	Reporting missed dose	30 (60.0)	
Curtin et al., 1999	USA	135 (46.7)	63.2 ± 13.8	AHT (n = 69), PB (74)	Self-report (BMQ)	Overdosing, under dosing, or missing an entire day's dose	AHT, 14 (20.3); PB, 34 (45.9)	CS (M)
					Pill count	Number of pills added at each refill	AHT, 63 (91.3); PB, 73 (98.6)	
					MEMS	Instance of bottle opening	AHT, 66 (95.7); PB, 72 (97.3)	

Note: Where studies has reported adherence rate for each medication or for more than one assessment method, these are reported in a separate row and are not addable. Therefore, the overall adherence rate does not account to more than 100%. Conversion factor for unit: SPL in mg/dL to mmol/L, x0.3229.

Abbreviations: AHG, antihyperglycemics; AHT, antihypertensives; AL, antilipidemics; BMQ, brief medication questionnaire; CM, calcimimetics; DDFQ, dialysis diet and fluid nonadherence questionnaire; DIPQ, drug intake percentage questionnaire; EMR, electronic medical record; HDS, herbal and dietary supplement; ISAI, Iowa self-assessment inventory; ITAS-M, modified immunosuppressive therapy adherence scale; LC, lanthanum carbonate; MAQ, medication adherence questionnaire; MARS, medication adherence report scale; MCA, multi-method compliance assessment (including: laboratory assessment, nurse assessment, and patient self-report); MEMS, medication event monitoring system; MGLT-4, Morisky 4-item Green Levine test; MMAS-8, Morisky 8-item medication adherence scale; MPR, medication possession ratio; PB, phosphate binder; SA, sevelamer hydrochloride; SMAQ, simplified medication adherence questionnaire; SPL, pre-dialysis serum phosphate level; Study design (CS, cross-sectional; P, prospective; R, retrospective); NA, not available.

[a]Effective public health practice project (EPHPP) quality assessment tool for quantitative studies. Study quality (S, strong; M, moderate; W, weak).

[b]Subsample of patients undergoing haemodialysis.

[c]Twelve industrialised countries (Australia/ New Zealand, Belgium, Canada, France, Germany, Italy, Spain, Sweden, and UK, twenty facilities each; Japan, sixty facilities; and USA, eighty facilities).

2.4.2. Assessment of Nonadherence

Half of the studies (n = 22) applied subjective measures exclusively, based on patients' self-reporting in order to assess nonadherence. However, the specific method of subjective assessment differed across studies. Thirteen studies used self-reporting measures with a validated questionnaire (Brief Medication Questionnaire (BMQ) [184], Drug Intake Percentage Questionnaire (DIPQ) [185], Modified Immunosuppressive Therapy Adherence Scale (ITAS-M) [154, 157], Medication Adherence Report Scale (MARS) [172, 174], Morisky 4-item Green Levine Test (MGLT-4) [150, 175, 180], Morisky 8-item Medication Adherence Scale (MMAS-8) [186], Medication Adherence Questionnaire (MAQ) [177], and Simplified Medication Adherence Questionnaire (SMAQ)) [173, 176, 185], whereas 9 studies utilised self-reporting via patient interviews or non-validated questionnaires [159-161, 165, 167, 181, 182, 190, 191].

Studies solely utilising biochemical measures of assessing nonadherence, based on pre-dialysis SPL, accounted for less than 25.0% (n = 10) of our included sample [33, 145, 158, 166, 168-171, 179, 183]. Furthermore, the least utilised method of assessing nonadherence to medication in patients undergoing haemodialysis was directly (13.6%, n = 6), that included either pill count or using electronic monitoring devices [9, 152, 153, 155, 156, 162].

Five out of the six studies that used two or more instruments to measure nonadherence employed subjective (patient self-reporting) and biochemical measures (pre-dialysis SPL) [164, 178, 187-189]. The one remaining study [163] integrated subjective with objective measures such as pill count and electronic monitoring system, respectively.

2.4.3. Definitions of Nonadherence

Studies reported wide variation in the definitions for each (subjective, objective, and biochemical) measure of nonadherence.

Subjective measures that used validated questionnaires defined nonadherence based on adherence rating scales [33, 154, 157, 170, 172, 174, 186, 187]. On the contrary, studies relying on non-validated questionnaires or interviews defined nonadherence via self-reported missed doses [159-161, 164, 165, 167, 190], cost-related medication non-purchase [191] or discrepancies in the self-reported adherence and prescription records [181, 182].

For objective measures, the nonadherence definition was based on pill count (taking less than 80% [9] of the prescribed medication), prescription refill frequency [153], instances of bottle opening as detected by using medication event monitoring devices [162, 163], and the medication possession ratio (MPR), defined as the number of doses dispensed in relation to the dispensing period with a cut-off value of 80% [152, 155, 156].

Studies considering biochemical measures for estimating nonadherence showed variation in their definitions. The upper limit of the acceptable range for pre-dialysis SPL was reported as being from 4.5 mg/dL [164, 171] to 7.5 mg/dL [145]. However, most of the studies (66.7%, n= 10) considered pre-dialysis SPL acceptable at the upper limit of 5 mg/dL [33, 169, 176, 183, 187, 188] to 5.5 mg/dL [168, 170, 177-179, 189]. A clinical proxy measure, such as SPL, is often influenced by clinical variables and dietary intake and, therefore, could confound an exploration of the relationship between serum phosphate and adherence outcomes [33]. During our

analysis we found five studies that employed both pre-dialysis SPL and patient self-reporting measures to assess adherence outcomes [164, 178, 187-189] (**Table 5**).

2.4.4. Prevalence of Nonadherence to Medication

In general, rates of nonadherence to medication in patients undergoing haemodialysis ranged from 12.5% to 98.6%. This variation was primarily observed due to different measures and definitions employed in estimating nonadherence rates. **Figure 10** shows the prevalence rates of medication nonadherence in patients undergoing haemodialysis according to the three subgroup measures of adherence (subjective, objective and biochemical), and also consolidates prevalence rates for similar measures within the three overarching subgroups.

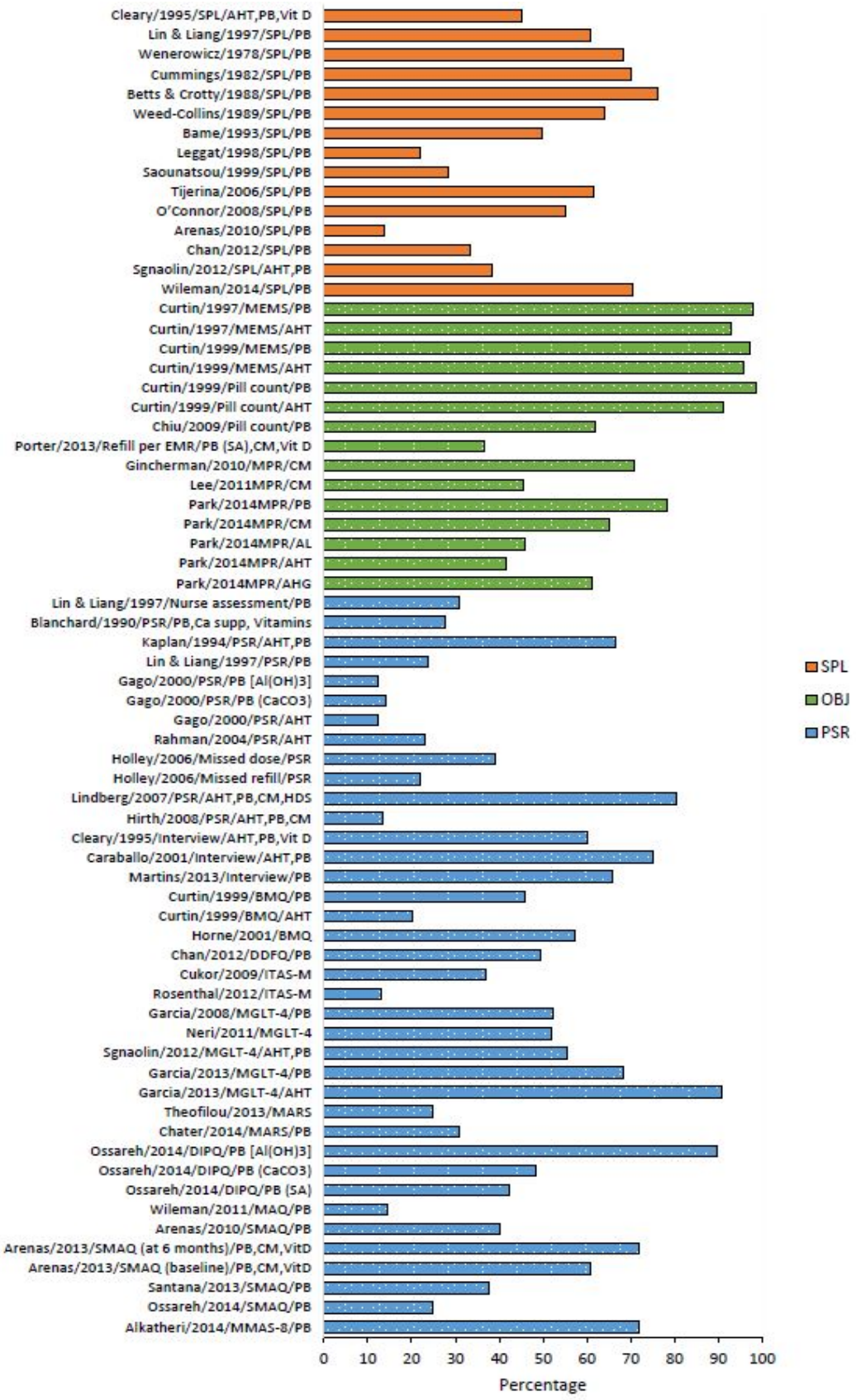

Figure 10: Prevalence rates of medication nonadherence in HD patients

Abbreviations: AHG, antihyperglycemics; AHT, antihypertensives; AL, antilipidemics; BMQ, brief medication questionnaire; CM, calcimimetics; DDFQ, dialysis diet and fluid nonadherence questionnaire; DIPQ, drug intake percentage questionnaire; EMR, electronic medical record; HD, haemodialysis; HDS, herbal and dietary supplements; ITAS-M, modified immunosuppressive therapy adherence scale; MARS, medication adherence report scale; MGLT-4, Morisky 4-item Green Levine test; MMAS-8, Morisky 8-item medication adherence scale; MPR, medication possession ratio; MAQ, medication adherence questionnaire; MEMS, medication event monitoring system; OBJ, objective measure of adherence; PB, phosphate binders; PSR, patient self-reported adherence; SA, sevelamer hydrochloride; SMAQ, simplified medication adherence questionnaire; SPL, pre-dialysis serum phosphate levels.

The most frequently studied renal-specific medications were phosphate binders (76.1%, n = 35), with eight studies [9, 153, 172, 173, 176, 178, 182, 185] specifically mentioning the types of phosphate binders prescribed (aluminium hydroxide, calcium acetate, calcium carbonate, lanthanum carbonate, and sevelamer hydrochloride). Other medications studied included, antihypertensives (27.3%, n = 12) and, calcimimetics (17.4%, n = 8). Fewer studies (9.1%, n = 4) estimated nonadherence to antidiabetic agents, antidyslipidaemic drugs, and calcium and vitamin D supplement products. Six studies did not specifically mention the types of medications studied [150, 154, 157, 159, 174, 184].

Nonadherence to phosphate binders ranged from 13.9 – 98.6%, with an average of 52.5%. The mean percentage of patients classified as non-adherent assessed by pre-dialysis SPL, subjective measures and objective measures, was 28.6%, 47.9% and 78.4%, respectively.

The estimates of nonadherence to antihypertensive medication in patients undergoing haemodialysis ranged between 12.5% and 95.7% (mean 38.2%). When assessed using different measures of nonadherence, such as patient self-reporting

and objective measures, the mean prevalence rates were 24.3% and 38.5%, respectively. The rate of nonadherence to other medications, such as antidiabetics and antidyslipidaemics, was 61.2% and 46.0%, respectively.

Among five studies [164, 178, 187-189] that used composite methods for measuring adherence, the rates of nonadherence varied greatly depending on the types of adherence measures used. The rates of nonadherence were lower when assessed using pre-dialysis SPL (ranged from 13.9% to 45.1%), whereas the same studies reported higher rates of nonadherence when using patient self-reporting measures (ranging from 40.0% to 60.0%) [164, 178, 187, 189]. The opposite was true in one study which showed that the rate of nonadherence was higher with pre-dialysis SPL (61.0%) and lower with patient self-reporting measures (23.6%) [188] (**Table 5**).

2.4.5. Factors Associated with Nonadherence

A total of 38 studies reported factors associated with nonadherence in patients undergoing haemodialysis. Data synthesis on the factors associated with nonadherence was based on the statistical significance and direction (positive or negative) of the association. The majority of studies relied on a univariate analysis to explore the factors associated with nonadherence, with only 15 studies using multivariate analyses [9, 33, 145, 150, 152, 154, 155, 157, 166, 172, 177-179, 185, 187]. A quantitative summary of statistically significant factors and their logical categorisation is presented as **Table 6**.

Table 6. Factors associated with nonadherence (n = 38)

Factors	No of studies	Significant association with measures of nonadherence[a]			References
		SPL	PSR	PC/ MEMS	
Socio-demographic variables					
Age	27				
Younger		8	8		[33, 150, 153, 166, 169, 170, 172, 177, 178, 181, 185-187, 189]
Older		1	2	1	[9, 145, 157, 174]
Gender	22				
Male			1		[185]
Female			2		[150, 177]
Low education (≤ high school)	15		1		[186]
Ethnicity (non-Caucasian)	7	1	1	2	[145, 162, 163, 172]
Marital status (single, divorced or widowed)	6		2		[174, 186]
Employment status (unemployed)	6		1		[174]
Lack of support from health care provider	2		2		[150, 170]
Family problems (illness interfering with family life)	2		1		[170]
Smoker	1	1			[145]
Clinical variables					
Long-term on HD	16		3		[150, 174, 187]
Comorbidity (DM, HTN)	9	1	1		[178]
Number of hospitalisation	2		1		[150]
Psycho-social variables					
Depressive symptoms	6		4		[154, 157, 174, 185]
Belief about medicine	5				
Concern		1	2		[172, 177, 184]
Benefit		1	1		[170]
Necessity		1	3		[33, 172, 177]

Factors	No of studies	Significant association with measures of nonadherence[a]			References
		SPL	PSR	PC/ MEMS	
Necessity-concern differential score			2		[33, 177]
Health locus of control[b]	3	2	1		[171, 188]
Internal			1		[174]
Doctors			1		[174]
Emotional representation	1	1			[179]
Medication related factors					
Poor knowledge about medicine	5	1	1		[170, 187]
Number of prescribed medicines	3			1	[162]
Daily tablet count	2	1	1		[150, 178]
Total no of PB prescribed	2	1	1		[178]
Total pill burden	2		1	1	[9, 150]
Pill burden from PB	1			1	[9]
PB equivalent dosage	1	1			[33]
Regimen complexity (frequency and dosage schedule)	1	1			[170]
Drug coverage by insurance	1			1	[152]
Health care cost (inpatient)	1			1	[155]

Abbreviations: DM, diabetes mellitus; HD, haemodialysis; HTN, hypertension; MEMS, medication event monitoring system; PB, phosphate binders; PC, pill count; PSR, patient self-report; SPL, pre-dialysis serum phosphate level.

[a]Level of significance ($p < 0.05$, $p < 0.01$, and $p < 0.001$) varies between studies.

[b]Defined as having high expectation that one's actions will have a causal relationship with the consequences produced.

Taking into account the relative number of studies that explored variables associated with nonadherence and the actual studies that found a significant association, we have identified a number of variables that are likely to influence medication adherence in patients undergoing haemodialysis. A number of demographic factors were found to be significantly associated with nonadherence. Age was one of the most frequently reported variables. Although younger age was commonly associated with nonadherence, four studies found nonadherence prevalent

in the older population as well. Other factors significantly associated with measures of nonadherence were: non-Caucasian ethnicity, illness interfering with family life, being a smoker, and being single, divorced or widowed. Very few studies found female gender, low education, and unemployment to be significantly associated with nonadherence. Support from healthcare providers had a significant positive effect on adherence to medication therapy.

Longevity of haemodialysis (five or more years on dialysis) was reported as the most common clinical factor but only three studies [150, 179, 187] found it to be significantly associated with nonadherence. Other clinical variables influencing adherence were having a concomitant illness like diabetes and hypertension, and recurrent hospitalisation (**Table 6**).

The psycho-social variables that were identified to influence nonadherence included: depressive symptoms, negative belief about medicines (concern, benefit, necessity, and necessity-concern differential score, calculated by subtracting the concerns subscale scores from the necessity subscale score, where the negative scores indicate that patients rate their concerns about medication above their beliefs in the necessity of taking it) [33, 170, 172, 177, 184], health locus of control, defined as having a high expectation that one's actions will have a causal relationship with the consequences produced [171, 174, 188], and emotional representation, that is emotional distress specific to the illness (**Table 6**).

Overall, nine studies [9, 33, 150, 152, 155, 162, 170, 178, 187] reported medication-related factors that were found to be significantly associated with nonadherence. These included daily tablet count, knowledge of medicines, total pill burden, total number of phosphate binders prescribed, phosphate binder equivalent

dosage (the relative phosphate binding coefficient based on the weight of each binder that can be estimated relative to calcium carbonate), pill burden from phosphate binder, medication regimen complexity (frequency and dosage schedule), drug coverage by insurance, and health care cost as inpatients (**Table 6**).

Fewer studies [33, 170, 178] evaluated factors associated with nonadherence using more than one measure of nonadherence (pre-dialysis SPL and patient self-reporting). The factors that showed significant correlation with both patient self-reported adherence and pre-dialysis SPL were: age [33, 178], comorbidity [178], total number of phosphate binders prescribed [178], belief about phosphate binder medicine (necessity) [33], and beliefs about medicine (benefits) [170]. However, beliefs about phosphate binder medicine (concern) were not significantly associated with both measures of adherence [33]. The study suggested that although patients had some concerns about their phosphate binder medicines, this did not appear to consistently influence their medication-taking behaviour.

2.4.6. Perceived Barriers of Adherence to Medication

Eight studies reported patients' perceived barriers to adherence to medication therapy. The most common reasons given by the patients to explain nonadherence were forgetfulness (n = 6 studies), poor tolerance of side effects (n = 4 studies), pill burden (n = 3 studies), and large tablet size (n = 2 studies). Other reasons included unpalatable taste, medication regimen complexity (frequency and dosage schedule), difficulty opening the medication container, prescription refilling, medication cost, transportation, knowledge of phosphate binder medicines, diet and fluid restrictions, knowledge of the importance of taking medicines, lack of interest, monotony, being away from home, and social discomfort [159, 160, 164, 165, 168, 173, 176, 187].

2.4.7. Study Quality

Based on the EPHPP Quality Assessment Tool, most studies (n = 41) were rated as being of moderate quality (**Table 5**). The reasons behind this moderate rating were, weak study design largely based on cross-sectional data [9, 33, 158-161, 163-166, 168-175, 177, 178, 180-191], using non-validated measures of data collection such as patient interviews or the lack of reliable data from the use of validated measures [153, 154, 157, 159-161, 163-165, 167, 172-176, 180-182, 185, 186, 189-191], and failure to report withdrawals and dropout rates of participants completing the study [145, 150, 152, 153, 155-159, 165, 166, 168, 170-172, 178-183, 185, 188, 191].

2.5. Discussion

The present systematic review summarised findings from 44 studies over a period of three decades to identify factors associated with nonadherence to medications in patients undergoing haemodialysis. Given the absence of a unified standardised approach to measuring nonadherence [192], the current review observed significant variability in the methodological quality of included studies.

A number of methods of assessing nonadherence to medication were observed in this review, such as objective measures of pill count, subjective measures of patient self-reporting and biochemical methods of measuring pre-dialysis SPL. Half of the studies exclusively applied subjective measures based on patients' self-reporting to assess nonadherence, compared with the two previous reviews [11, 147] that reported measurement of SPL as the most frequent method. These changes may be due to the

availability of validated medication adherence scales to measure nonadherence in clinical practice [193]. Additionally, limitations of SPL are increasingly being recognised as it can be influenced by non-medication related factors, such as adherence to dietary restrictions, dialysis attendance, residual renal function, hormonal and acid-base balance, and the type and intensity of dialysis treatment [11, 194].

Discrepancies in defining nonadherence were observed among studies that used subjective measures with non-validated questionnaires [159-161, 164, 165, 167, 190], and biochemical measures like pre-dialysis SPL [145, 164, 171]. Owing to these inconsistent definitions, a wide variation in the reported rates of nonadherence was observed. A study defining the acceptable range of pre-dialysis SPL at a higher cut-off value of 7.5 mg/dL reported the lowest rates of nonadherence (22.1%) [145], whereas the study adopting a lower cut-off value of 4.5 mg/dL reported one of the highest rates of nonadherence (68.4%) [171]. Combining information across studies becomes problematic when a patient defined as adherent, based on certain criteria in one study, would be defined as non-adherent, based on different criteria in another study [195]. Hence, there is a need for a consensus on defining or assessing medication adherence to study the problem effectively, to understand the underlying factors, and to develop and test interventions to improve adherence.

Overall, the prevalence rates of nonadherence to medication ranged between 12.5% and 98.6%, which is comparatively higher than with other chronic conditions such as diabetes (prevalence rates ranged from 6.9% to 61.5%) [47], schizophrenia-spectrum disorders (5.0% to 52.8%) [45], and chronic skin conditions such as psoriasis (33.4% and 78.4%) [57]. Nonadherence rates in patients undergoing haemodialysis are higher in comparison with other dialysis modalities such as peritoneal dialysis (PD)

that ranged from 3.9% to 43.0% [25]. These divergent findings between two modalities of dialysis treatment might have been influenced by the intermittent nature of maintenance haemodialysis sessions that require more stringent dietary and medication requirements as compared with PD. Other factors include that PD is often a starter therapy, and patients may not have been sick for as long as those on haemodialysis [196]. Also some PD patients receive kidney transplant or eventually switch to haemodialysis. This often selects out a younger population who may have a lesser dialysis vintage, as well as a disparity in health literacy and dialysis knowledge [137].

A number of demographic and clinical factors were found to be significantly associated with nonadherence. Not surprisingly, the findings correspond with the results of a systematic review of determinants of patient adherence conducted by Kardas et al [197]. Besides that, different aspects of beliefs about medicines were found to be possible barriers for adherence; this includes necessity, concerns, and benefits from the medication therapy. Patients who expressed lower necessity beliefs and greater concerns about potential adverse effects of medications were more likely to be nonadherent [33, 170, 172, 177, 184]. A significant majority of patients undergoing haemodialysis is prescribed with phosphate binders and antihypertensive medications; these account for high pill burden [9], are associated with adverse effects, and result in nonadherence [9]. Phosphate binders often cause constipation and gastrointestinal discomfort to the patients [198]. Similarly, antihypertensive medicines potentially add to hypotension post-dialysis treatment [199], and patients can cease these medications due to the haemodynamic effects they experience. Therefore, taking account of patients' beliefs about necessity and concerns about

medicines is essential to support informed choice and optimal adherence to prescribed treatment [200].

The need for lifelong and complex medication regimens can contribute to nonadherence [139]. Surprisingly, among the nine studies that assessed medication-related factors, only one study identified that medication regimen complexity (frequency and dosage schedule) was significantly associated with nonadherence [170]. Medication regimen complexity can be measured with the Medication Regimen Complexity Index (MRCI), a validated instrument developed by George et al [201]. Unfortunately, in most chronic illness, including ESKD, researchers have not measured regimen complexity until recently [202]. Change in MRCI scores following an intervention has been studied in diabetic, elderly and home haemodialysis patients [203-205]. Initiatives aiming to improve medication adherence should consider the above-mentioned determinants to ensure that patients are actively involved in designing medication regimens considering the relative contribution of each medicine to the regimen complexity.

This study has some limitations. They are mostly related to the original studies included in this review. The majority of the reviewed studies were cross-sectional in design and, considered to be of limited suitability for assessing adherence behaviour [45]. Furthermore, the reverse causation bias (which suggests that the direction of cause and effect may be difficult to assess: Did the “outcome” affect the measured exposure level or did the exposure affect the outcome?) [206] cannot be ruled out in cross-sectional studies. Therefore, readers are encouraged to exercise caution in the interpretation of the findings from this review. An examination of clinical outcomes and consequences of nonadherence to medication therapy was beyond the scope of this review. Due to time and resource limitations, we predominantly relied on the full-text

articles published in peer-reviewed journals and did not search conference proceedings for relevant abstracts. Nevertheless, the studies included in this review represent a diverse community of patients from wide geographic locations. Furthermore, more than half of the included studies had large sample sizes of over 100 participants.

2.6. Conclusion

Nonadherence to medication therapy is a significant issue in patients undergoing haemodialysis. Differences in definitions and tools to measure nonadherence are widespread in the current literature. This necessitates a consensus on defining or assessing medication nonadherence in order to study underlying issues effectively, to understand barriers to adherence properly, and to develop and test intervention measures in order to improve adherence in patients undergoing haemodialysis. Abiding by the definition of clinical targets for biochemical measures, such as pre-dialysis SPL, as recommended by international clinical practice guidelines (for example, Kidney Disease Improving Global Outcomes (KDIGO), National Kidney Foundation- Kidney Disease Outcomes Quality Initiative (NKF- KDOQI) or Kidney Health Australia- Caring for Australasians with Renal Impairment (KHA- CARI)) and adapting a consistently measured method to assess medication nonadherence can be promising steps. Also, triangulation can be tried when objective data are available for assessment. Clinicians should be aware of different strategies to promote adherence in this unique patient group, including reducing the pill burden, being aware of potential adverse effects of medications which promote nonadherence, and other strategies such as using combination products. It is also imperative to improve education

regarding the patient's medication regimens, and to provide concise instructions to prevent confusion. Future research should be directed towards more rigorous approaches, such as a prospective longitudinal study design, and should aim towards developing standard definitions and validating available measurement tools, while focusing on the role of additional factors such as psychosocial and behavioural factors in predicting nonadherence to medications.

Supporting Information

Appendix 1. PRISMA Checklist.

Appendix 2. Electronic search strategy.

CHAPTER THREE

3. MEDICATION REGIMEN COMPLEXITY AND ADHERENCE IN HAEMODIALYSIS PATIENTS: AN EXPLORATORY STUDY

3.1. Abstract

Background. The impact of medication regimen complexity on adherence in patients undergoing haemodialysis is unknown. We investigated regimen complexity, perceived burden of medicines (PBM), and health-related quality of life (HR-QoL) as potential predictors of adherence.

Methods. Adult (≥ 18 years) patients undergoing haemodialysis were recruited from outpatient dialysis centre, Hobart, Australia. Data on medication regimen complexity index (MRCI), self-reported and objective adherence, comorbidity index, PBM, and HR-QoL were obtained using established measures. Socio-demographic and clinical characteristics were collected during interviews and by reviewing medical records. Predictors of adherence were determined using logistic regression.

Results. Fifty-three out of 70 patients undergoing haemodialysis participated (response rate, 75%; male, 58.5%; age, 67.9±11.5 years). The mean MRCI, HR-QoL, and PBM scores were 27.0±10.9, 0.70±0.13 and 1.7±0.6, respectively. Based on self-reports, 43.4% (n = 23) were adherent, whereas for subset of patients analysed using objective measure (n = 33), much lower adherence rate was observed (27.3%, n = 9). The self-reported and objective measure were significantly correlated (r = 0.43, p = 0.01). Older age was the only significant predictor of self-reported adherence (odds ratio [OR], 1.05; 95% CI, 1.00–1.11) whereas, older age (OR, 1.10; 95% CI, 1.00–

1.21), higher comorbidity (OR, 1.58; 95% CI, 1.03–2.42) and MRCI (OR, 1.14; 95% CI, 1.02–1.27) were independent predictors of objective adherence.

Conclusions. The findings of this exploratory study suggest that older patients with high comorbidities and highly complex regimen are more likely to be adherent based on an objective measure. Future research is needed using objective measures of adherence suitable for all patients and reflecting all medications.

Keywords: Adherence; chronic kidney failure; haemodialysis; health-related quality of life; medication regimen complexity; perceived burden of medicines

3.2. Introduction

Medication nonadherence is associated with poor patient outcomes and costs approximately US $100 billion a year [2]. The estimated prevalence of medication nonadherence in patients undergoing dialysis ranges between 12.5% and 98.6% [23]. A recent Australian study on research priorities in chronic kidney disease (CKD) identified simplifying medication regimens as one of the topmost priorities in patients undergoing haemodialysis, to facilitate adherence [207]. A number of comorbidities often co-exist with end stage kidney disease (ESKD), with diabetes and cardiovascular disease being the most common [8]. Additionally, complications more frequently noted in patients undergoing dialysis are imbalances in calcium and phosphate haemostasis, anaemia, hyperlipidaemia, and secondary hyperparathyroidism [23, 139]. Owing to these comorbid conditions and dialysis-related complications, patients undergoing dialysis often have a high pill burden, with a median number of prescribed medications ranging between 12 and 19 per day [9]. The additional complexity of medication regimens, such as variation in the dosing frequency, differences in the prescribed dosage forms and administration instructions, further add to the regimen complexity and predispose these patients to a high risk of medication nonadherence [140, 201, 202, 204, 208].

Medication regimen complexity and perceived burden of medicines (PBM) have been noted as potential contributors to medication nonadherence in chronic diseases [150, 202]. An Italian study conducted in patients undergoing haemodialysis found an inverse relationship between regimen complexity (as defined by the number of medicines prescribed), patients' PBM and self-reported adherence [150]. In another instance, high pill burden posed by phosphate binders significantly lowered medication adherence and affected health-related quality of life (HR-QoL) in patients undergoing

haemodialysis [9]. Medication regimen complexity index (MRCI) is one of the most frequently used instruments that provides an objective assessment of a regimen complexity in a given patient [201]. However, only a small number of studies have assessed regimen complexity using the MRCI tool in chronic illnesses, including ESKD [202]. A significant increase in MRCI scores was observed over time when patients were switched from hospital-based to home-based haemodialysis modality [203]. To the best of our knowledge, studies exploring regimen complexity as a likely determinant of medication adherence in patients undergoing haemodialysis are lacking. The primary aim of this research was to determine the association between the medication regimen complexity and medication adherence in patients undergoing haemodialysis. A secondary aim was to examine the association between regimen complexity and patients' PBM and HR-QoL.

3.3. Methods

This was a cross-sectional study of patients undergoing haemodialysis at the outpatient dialysis unit, Hobart, Tasmania, Australia. The unit comprises 20 dialysis chairs and operates daily with two in-centre daytime haemodialysis sessions. Patients undergo three dialysis sessions of up to 5 hours each, per week. Seventy patients with ESKD were receiving haemodialysis during the study period between February and June 2015.

3.3.1. Data Collection

All 70 adult (≥ 18 years) English speaking patients receiving haemodialysis were invited to participate in the study. Consented patients were interviewed by a

pharmacist researcher to obtain a comprehensive medication history, as per the guidelines of the Australian Commission on Safety and Quality in Health Care on medication history taking [209]. The accuracy of the medication history was verified by reviewing patients' medical records.

Regimen complexity was assessed using the validated 65-item medication regimen complexity index (MRCI) tool [201]. The MRCI is divided into three sections covering pharmaceutical dosage forms, dosing frequency, and additional instructions. The minimum MRCI score for someone on medication is 1.5, which represents a single tablet or capsule taken once a day when needed while there is no established maximum as the score increases in line with the increase in regimen complexity. Daily pill burden (or number of pills taken daily) was calculated based on total number of pills (including tablets, capsules, injections, inhalations, etc.) prescribed for patients to be taken on a daily basis, but excluding medications that contained instructions like 'as directed' or 'on prn basis'.

Data on self-reported medication adherence was obtained using the 4-item Morisky scale [20, 150]. Patients having a Morisky score of zero were defined as adherent in this study, similar to other studies assessing self-reported adherence [150]. Objective adherence was measured using the mid-week, pre-dialysis serum phosphate levels (SPL) in the sub-group of patients who were prescribed phosphate binders, in line with adherence studies conducted in patients undergoing haemodialysis [33]. Patients were considered to be nonadherent when the average of the monthly pre-dialysis SPL (past 3 months from data collection) exceeded 1.6 mmol/L, based on the recommendations from Kidney Health Australia – Caring for Australasians with Renal Impairment (KHA-CARI) guidelines [210].

PBM and HR-QoL were measured using a validated 6-item Burden of Oral Therapy (BOT) scale [150] and EQ-5D-5L, a standardised instrument developed by the EuroQoL group [211], respectively. The BOT items were rated on a 5-point Likert scale, with 1 considered not at all bothered and 5 considered extremely bothered. The EuroQoL-5D descriptive system is composed of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels ranging from 1-5, where 1 means no problem and 5 means an extreme problem with a particular dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. EQ-5D-5L index value sets for the Australian population are not available, and the United Kingdom value sets were used as per the recommended practice in measuring the quality of life [212, 213].

Data on Charlson's comorbidity index [214], years on dialysis, the number of hospitalisations, and dialysis sessions missed in the preceding 12 months were collected from patients' medical records. Data on socio-demographic variables, such as age, gender, highest education, employment status, marital status and smoking history, were obtained through interview and confirmed, where possible, from the medical records. The study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (HREC approval number H0014506) and the work was performed in accordance with the Declaration of Helsinki.

3.3.2. Statistical Analysis

Statistical analysis was performed using SPSS Version 21.0 (IBM Corp., Armonk, NY, USA). Mean with standard deviation was used to summarise continuous variables and independent samples t-tests were used for inferential analyses, whereas

frequencies and percentages were calculated for binomial data and Chi-squared tests were used for inferential analyses. Correlations between the study variables were tested using Pearson's correlation coefficient. Study variables with probability (p) values $\leqslant$ 0.10 in the univariate analysis were entered into the multivariate logistic regression model to identify predictors of self-reported and objective adherence. A p-value of < 0.05 was considered statistically significant.

3.4. Results

Fifty-three out of 70 patients undergoing haemodialysis provided consent to participate (response rate, 75%). Socio-demographic and clinical characteristics of non-participants were not available due to ethical considerations however the reason for nonparticipation was mainly due to disinterest, inconvenience or tiredness. More than half of the patients were male (58.5%, n = 31) and the mean age was 67.9±11.5 years.

Patients, on average, were prescribed 11.1 ± 4.2 medications, with a daily pill burden of 16.3 ± 6.9 pills. More than half (58.5%, n = 31) of the patients were taking, at least, one antihypertensive medication, followed by medications for anaemia (50.6%, n = 27) and ischaemic heart disease (47.2%, n = 25). The most common medicines prescribed were aspirin (56.6%, n = 30), sevelamer hydrochloride (49.1%, n = 26), paracetamol (37.7%, n = 20), esomeprazole and allopurinol (each 30.2%, n = 16), and furosemide (28.3%, n = 15). Among the patients prescribed phosphate binders, more than two-thirds were taking sevelamer hydrochloride, with an average dosage of 3200 mg/day (78.8%, n = 26), followed by aluminium hydroxide (15.2%, n = 5; average dosage 1920 mg/day) and lanthanum carbonate (6.1%, n = 2; average dosage 3000 mg/day). Few patients (11.3%, n = 6) had missed at least one dialysis session in the

preceding 12 months while most patients (64.2%, n = 34) had had at least one unplanned hospital admission during the same period (**Table 7**).

Table 7. Study Characteristics based on Patient Self-reported Adherence

Variables	**Total cohort (*n* = 53)**	**Adherent (*n* = 23)**	**Nonadherent (*n* = 30)**	***P***
Age (years)	67.9±11.5	71.7±11.1	64.9±11.1	0.03
Gender (male)	31 (58.5)	15 (65.2)	16 (53.3)	0.3
Education (≥ high school)	40 (75.5)	15 (65.2)	25 (83.3)	0.1
Employment (unemployed)	47 (88.7)	22 (95.7)	25 (83.3)	0.1
Marital status (married)	37 (69.8)	19 (82.6)	18 (60.0)	0.1
Living with family	39 (73.6)	18 (78.3)	21 (70.0)	0.4
Smoking history (non-smoker)	44 (83.0)	20 (87.0)	24 (80.0)	0.5
Years on dialysis	3.7±3.4	3.7±4.0	3.7±2.9	0.9
Charlson's comorbidity index	6.3±2.1	6.8±1.9	5.9±2.2	0.1
Pre-dialysis SPL (mmol/L)	1.7±0.5	1.5±0.4	1.9±0.5	0.01
Dialysis session missed^{+}	6 (11.3)	2 (8.7)	4 (13.3)	0.5
Hospitalisation (past one year)$^{\mu}$	34 (64.2)	14 (60.9)	20 (66.7)	0.6
Patients prescribed with PB	33 (62.3)	11 (47.8)	22 (73.3)	0.05
Number of medicines prescribed	11.1±4.2	11.3±4.1	10.9±4.4	0.7
Daily pill burden$^{\beta}$	16.3±6.9	16.2±6.4	16.3±7.4	0.9
MRCI (total score)	27.0±10.9	27.9±12.2	26.3±10.1	0.6
EQ-5D-5L index	0.70±0.13	0.71±0.14	0.69±0.12	0.6
Perceived burden of medicines	1.7±0.6	1.6±0.6	1.8±0.6	0.1

Note: For continuous variables, mean±SD and p-value indicated from t-test; for categorical variables, frequency (numbers with percentages in parentheses) and p-value indicated from Chi-squared test;

EQ-5D-5L, developed by EuroQol group for the measurement of health-related quality of life. The index value sets lies between 0 and 1, where one represents best possible health and zero is equivalent to death. A negative valuation can be given for certain health states regarded as being worse than death. Abbreviations: MRCI, medication regimen complexity index; PB, phosphate binders; SPL, pre-dialysis serum phosphate level (averaged over 3 months prior to the month of data collection).

[+] At least one dialysis session missed, past one year prior to the month of data collection. Study cohort missing ≥ 2 sessions past one year were less than 5% (n = 2).

[μ] At least one event of hospitalisation, past one year prior to the month of data collection. Study cohort having ≥ 2 events of hospitalisation past one year were 41.5% (n = 22).

[β] The number of tablets, capsules, or other dosage forms that a person takes on a regular basis.

Less than half of the patients were adherent to prescribed medications (43.4%, n = 23) as assessed by self-reported measure. The mean age of adherent patients was significantly higher than the nonadherent ones (**Table 7**). The MRCI value in the studied population showed a mean score of 27.0±10.9 (range, 9.5–55.0). The most relevant factors contributing to the final score of regimen complexity were dosing frequency ($r = 0.93$, $p < 0.001$) and additional instructions given for taking medications ($r = 0.84$, $p < 0.001$), followed by pharmaceutical dosage forms ($r = 0.74$, $p < 0.001$). The number of medicines prescribed, daily pill burden and MRCI scores did not differ between adherent and nonadherent patients while a significant number of patients prescribed with phosphate binders (73.3%, n = 22) were found to be nonadherent on self-reports (**Table 7**).

Among the patients prescribed phosphate binders, adherence was determined using pre-dialysis SPL as an objective measure (n = 33). Only one-fourth of the patients (27.3%, n = 9) were considered adherent. The adherent patients had a significantly higher age, higher comorbidity index, daily pill burden and regimen

complexity scores (**Figure 11**). The self-reported and objective measure of adherence were significantly correlated in those taking phosphate binders (r = 0.43, p = 0.01).

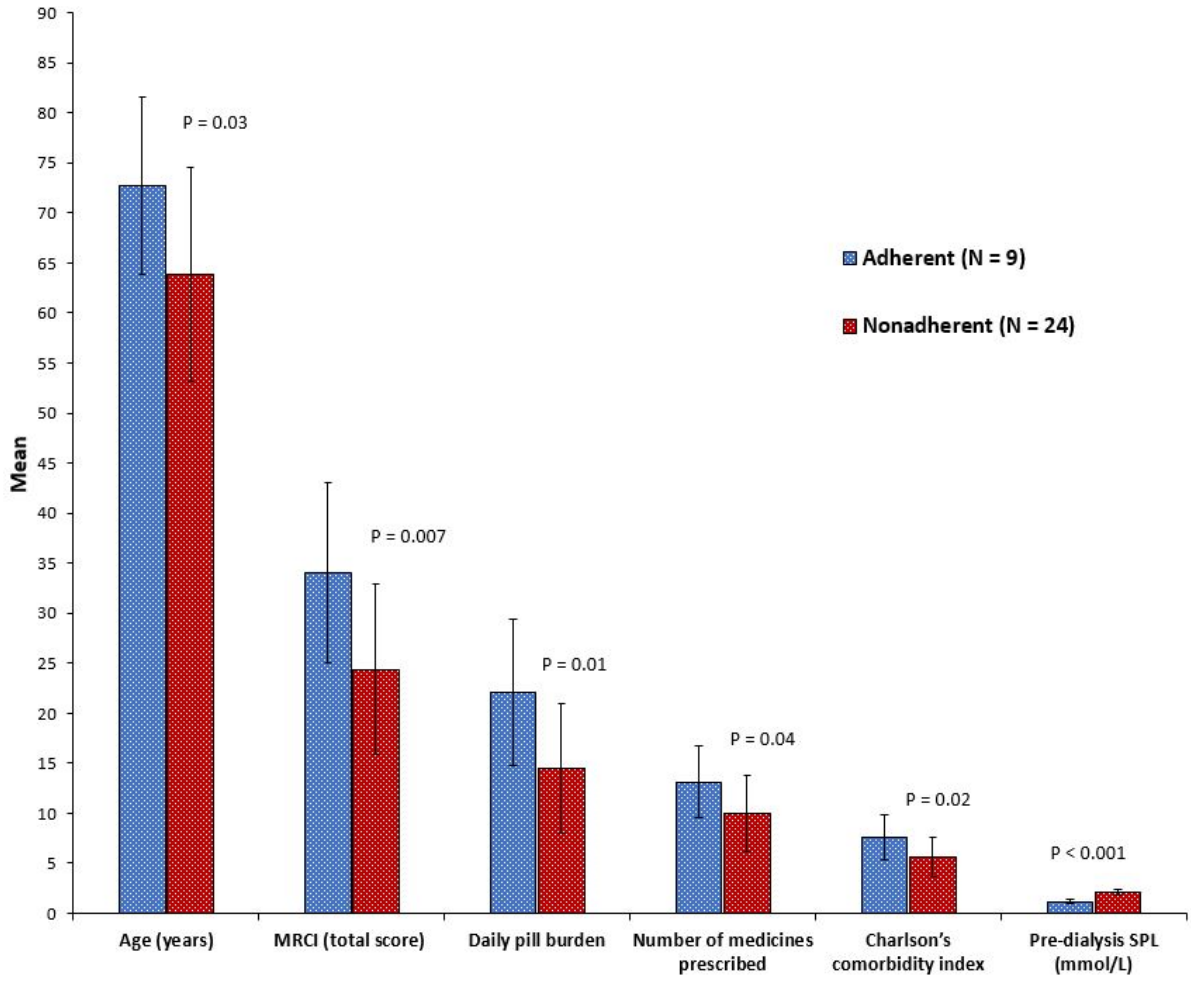

Figure 11. Characteristics of Patient Prescribed with Phosphate Binders (n = 33).

Adherence was determined using pre-dialysis serum phosphate levels (SPL) as a clinical proxy measure of adherence. Patients were considered to be nonadherent when the average of the monthly pre-dialysis SPL (past 3 months from data collection) exceeded 1.6 mmol/L, based on recommendations from Kidney Health Australia – Caring for Australasians with Renal Impairment (KHA-CARI) guidelines. For continuous variables, mean±SD and p-value indicated from t-test; MRCI, medication regimen complexity index.

The average PBM and HR-QoL scores were 1.7±0.6 and 0.70±0.13, respectively. The mean PBM scores were not different between adherent and nonadherent patients. Similarly, HR-QoL, as measured using EQ-5D-5L index, was not different between the adherent and nonadherent groups (**Table 7**).

Table 8 depicts the predictors of self-reported and objective adherence, as determined using logistic regression. The only significant predictor of self-reported adherence was old age (odds ratio [OR], 1.05; 95% CI, 1.00–1.11). Being married (OR, 3.17; 95% CI, 0.86–11.65) and prescribed with phosphate binders (OR, 0.33; 95% CI, 0.11–1.05) had a borderline significant association. Whilst, the analysis based on the objective measure identified higher regimen complexity (OR, 1.14; 95% CI, 1.02–1.27), increasing comorbidity (OR, 1.58; 95% CI, 1.03–2.42), and increasing age (OR, 1.10; 95% CI, 1.00–1.21) as the significant predictors of adherence. The PBM and HR-QoL scores were not associated with both measures of adherence.

Table 8. Predictors of Adherence using Logistic Regression Analysis

Variables	**Adjusted OR (95% CI)**	***P***
Predictors of self-reported adherence [a]		
MRCI (total score)	1.00 (0.95–1.06)	0.96
Age (per year)	1.05 (1.00–1.11)	0.04
Charlson's comorbidity index	1.22 (0.92–1.60)	0.16
Marital status (married)	3.17 (0.86–11.65)	0.08
Phosphate binders (prescribed)	0.33 (0.11–1.05)	0.06
Predictors of objective adherence [b]		
MRCI (total score)	1.14 (1.02–1.27)	0.02
Age (per year)	1.10 (1.00–1.21)	0.04
Charlson's comorbidity index	1.58 (1.03–2.42)	0.03

Note: Objective adherence was determined using pre-dialysis serum phosphate levels (SPL) as a clinical proxy measure of adherence (n = 33). Patients were considered to be nonadherent when the average of the monthly pre-dialysis SPL (past 3 months from data collection) exceeded 1.6 mmol/L, based on recommendations from Kidney Health Australia – Caring for Australasians with Renal Impairment (KHA-CARI) guidelines. Abbreviations: 95% CI, 95% confidence interval; MRCI, medication regimen complexity index; OR, odds ratio.

[a] Adjusted for age, Charlson's comorbidity index, marital status, and phosphate binders prescribed

[b] Adjusted for age and Charlson's comorbidity index

3.5. Discussion

We reported the role of medication regimen complexity on medication adherence in patients undergoing haemodialysis. A low rate of medication adherence (below 50%) was noted using self-reported and an objective measure of adherence. Higher regimen complexity, increasing comorbidity and increasing age were significant predictors of adherence using an objective measure, whereas only increasing age was associated with self-reported adherence. Being married and prescribed with phosphate binders depicted a borderline significant association. Interestingly, PBM and HR-QoL scores did not differ between adherent and nonadherent patients, using both the self-reported and an objective measure of adherence.

The mean MRCI score in this study was comparable to that reported in home haemodialysis patients [203], though expectedly much higher than the previous studies in non-ESKD (mean MRCI, 15.5) [215] and institutionalised elderly people (mean MRCI, 18.2) [216]. Our results of low rates of medication adherence among patients undergoing haemodialysis corroborated earlier findings [9, 11, 150]. We did not find any association between regimen complexity and self-reported adherence. This is in contrast to the only other study in patients undergoing dialysis that found an inverse association between regimen complexity and patient self-reported adherence. Notably, the study by Neri et al. [150] defined regimen complexity based on the number of pills prescribed daily and did not consider dosage forms, frequency of dosing and additional usage instructions; all of these factors are important contributors to a regimen complexity [201]. Although daily pill burden poses a threat to optimal adherence in patients undergoing haemodialysis [9], there is an equal possibility that having a few or many pills daily may result into equally high regimen complexity scores when all the dosage characteristics are considered. Moreover, we also found a strong

correlation between daily pill burden and MRCI scores ($r = 0.88$, $p < 0.001$). As such, we investigated the relationship between regimen complexity and adherence using the MRCI scores.

Lower rates of adherence to phosphate binders have been linked with the type of binders prescribed [217]. More than two-thirds of the patients prescribed with phosphate binders were taking sevelamer hydrochloride (SH) in our sample. SH has a large tablet size, is non-chewable, needs frequent dosing and poses a higher pill burden in patients as compared to lanthanum carbonate (LC) [218]. Optimising regimen with alternative phosphate binders has been found effective in previous studies. The daily pill burden from phosphate binders was reduced to half after changing from SH to LC, and the adherence rate increased from 46.9% at baseline to 72.5% at 12 months, with a significant decrease in the treatment cost incurred from phosphate binders [217].

We found younger patients more likely to be nonadherent as compared to their older counterparts, and this finding is in agreement with previous studies in dialysis patients [11, 23, 150]. This can be partly explained by the fact that older patients with multiple comorbidities may be more concerned about mortality and prefer structured lives and adhere to medication therapy [11], despite increasing polypharmacy and associated regimen complexity. On the other hand, younger patients often report treatment-related issues for having difficulty in coming to terms with chronic illness [11, 150] and might be at increased risk of nonadherence. On the contrary, increasing age, higher comorbidities and polypharmacy with complex regimen has been associated with poor medication adherence in other chronic diseases [44, 219]. Therefore, intervention programs targeting medication nonadherence often focus on older patients with multiple comorbid conditions [220]. It is extremely important that

intervention programs aimed at improving adherence in patients undergoing dialysis are mindful of the differences between other chronic conditions and ESKD, and should be more vigilant towards supporting younger patients undergoing dialysis.

Our study has some limitations. The eminent one being the single-centred study with small sample size and subset nature of the objective measure of adherence. Though we had a small number of patients prescribed with phosphate binders, a significant negative correlation ($r = – 0.26$, $p = 0.05$) between prescribing phosphate binders and patient self-reported adherence was observed. The objective measure of pre-dialysis SPL only considers phosphate binders whereas the MRCI incorporates all medications. Furthermore, the reliability of measuring pre-dialysis SPL can be questioned as it is subjected to dietary and clinical factors. Moreover, the value may also be influenced by the 'white-coat adherence' phenomenon [2]. To overcome this issue, we collected preceding 3 months routinely measured pre-dialysis SPL of patients from medical records to estimate objective adherence to phosphate binders. On the other hand, self-reported Morisky questionnaire can be susceptible to recall bias and also evoke a social desirability response in the patients, which may result in an overestimation of the actual adherence behaviour [32]. Nevertheless, in lack of a gold-standard tool for measuring adherence in clinical practice [208], we considered using both measures and found a relatively strong association between them, further assuring that our assessment of adherence was reliable [33, 221]. The cross-sectional nature of this study can limit the suitability of measuring adherence behaviour due to reverse causation bias [206]. However, an investigation of patients' preceding 12 months medical history revealed few patients having missed dialysis sessions while most patients had been hospitalised at least once for non-elective reasons, indicating that patients' non-responsiveness to therapy may be due to poor adherence and the

observed high nonadherence rates were not due to chance. Considering the exploratory nature of this study conducted in a small sample of patients undergoing haemodialysis, generalisability of the findings can be compromised. Therefore, we encourage readers for a cautious interpretation of our findings. Nonetheless, the regimen complexity scores, medication burden scores, demographic profiles and comorbidity scores identified in this study were similar to previous findings [9, 150, 203].

In conclusion, medication regimen complexity was not associated with patient self-reported adherence. Small subset of patients analysed using objective adherence measure found older patients having high comorbidity and highly complex medication regimens more likely to be adherent to their medications. Dialysis care professionals should be more vigilant towards supporting younger patients during their early adjustment to haemodialysis prescription. Future research should consider recruiting large sample of patients undergoing haemodialysis and using objective measures of adherence suitable for all patients and reflecting all medications (for e.g. medication possession ratio) to help confirm or not the exploratory findings of this study. Furthermore, future studies should explore the potential use of triangulation method whereby subjective and objective adherence assessment measures can supplement each other in determining the actual patient adherence to medication.

Supporting Information

Appendix 3. Patient Medication History Interview Questions

Appendix 4. Patient Self-reported Questionnaires

Appendix 5. Data collection form

Appendix 6. Medication Regimen Complexity Index, MRCI

CHAPTER FOUR

4. MEDICATION ADHERENCE PERSPECTIVES IN HAEMODIALYSIS PATIENTS: A QUALITATIVE STUDY

4.1. Abstract

Background: Medication nonadherence is highly prevalent among end-stage kidney disease patients undergoing haemodialysis. The aims of this study were to explore factors associated with medication adherence, and, to examine the differential perspectives on medication-taking behaviour shown by adherent and nonadherent patients undergoing haemodialysis, based on self-reported measures of adherence.

Methods: A qualitative exploratory design was used. One-on-one semi-structured interviews were conducted with 30 patients undergoing haemodialysis at the outpatient dialysis facility in Hobart, Australia. Patient self-reported adherence was measured using the 4-item Morisky Green Levine scale. Interview transcripts were analysed using a template analysis method and mapped against the World Health Organisation (WHO) determinants of medication adherence.

Results: Participants were 44-84 years old and were prescribed with 4-19 medications daily. More than half of the participants were nonadherent to their medications, based on self-reporting measure (56.7%, n = 17). Themes mapped against the WHO adherence model were patient-related (knowledge, awareness, attitude, self-efficacy, action control and facilitation), health system/ healthcare team related (quality of interaction, and mistrust and collateral arrangements), therapy-related (physical

characteristics of medicines, packaging, and side effects), condition-related (symptom severity), and social/ economic factors (access to medicines and relative affordability).

Conclusions: Patients expressed a number of concerns that led to nonadherence behaviour. Many of the issues identified were patient-related and potentially modifiable by using psycho-educational or cognitive-behavioural interventions. Healthcare professionals should be more vigilant towards identifying these concerns in order to address adherence issues. Future research should be aimed at understanding healthcare professionals' perceptions and practices of assessing medication adherence in patients undergoing dialysis that may guide intervention, in order to resolve this significant issue of medication nonadherence.

Keywords: End-stage kidney disease; haemodialysis; medication adherence; patients' perspectives; qualitative study

4.2. Introduction

An estimated 2.6 million people worldwide received dialysis treatment for end-stage kidney disease (ESKD) in 2010, and a two-fold increase is expected by 2030 [222]. Developing a new molecule into a medicine for clinical use costs about $2.6 billion [223], whereas the cost of treating complications from medication nonadherence averages about $100 billion a year [2]. Medication nonadherence is highly prevalent in ESKD patients undergoing haemodialysis with an average prevalence rate of 52.5% [23]. The consequences of medication nonadherence are detrimental and costly in patients undergoing haemodialysis [23, 191, 224], as these patients have an increased burden of co-existing illness and have been prescribed with multiple complex regimens [140, 202, 208, 225]. Younger age, higher comorbidities, frequent hospitalisations, poly-pharmacy, experience of side effects, and high pill burden have been consistently reported as predictors of low medication adherence in patients undergoing haemodialysis [8, 11, 23, 146]. These adherence predictors have been mainly identified through quantitative methods. However, these methods are less capable of exploring patients' perspectives on medication-taking behaviour and the challenges they face while adhering to their prescribed regimens [226]. There is a limited number of studies that have examined the patients' perspectives on renal failure, treatment adherence, dietary constraints, and phosphate binding medications [226-228]. To date, little is known about haemodialysis patients' perceptions regarding their prescribed regimen and the factors influencing their medication-taking behaviour. Understanding patients' perspectives can help identify potentially modifiable factors such as patients' intention to adhere, beliefs about medicines, features about treatment regimens, experiences of side effects, and provision of support mechanisms required to facilitate adherence [7]. As such, we aimed to explore qualitatively factors associated with

medication adherence, and to examine the perspectives on medication-taking behaviour, as shown by adherent and nonadherent patients undergoing haemodialysis.

4.3. Methods

4.3.1. Study Design

A qualitative exploratory design was used. The consolidated criteria for reporting qualitative research (COREQ) guideline [15] was followed during the conduct and reporting of the study (**Appendix 7**). Ethics approval was granted by the Tasmanian Health and Medical Human Research Ethics Committee (H0014506). Written informed consent was obtained from all the participants.

4.3.2. Research Team and Reflexivity

Interviews were conducted by a pharmacist researcher (SG). The interviewer was external to the study site, and both the participants and the interviewer were unknown to each other before the study. The study aims and professional status of the interviewer were discussed with the participants prior to conducting the interviews.

4.3.3. Participants

All adult (≥ 18 years), English speaking patients, undergoing haemodialysis at the outpatient dialysis unit in Hobart, Australia were eligible to participate. Participant recruitment was sought from patients who had earlier participated in a cross-sectional

study [229] that investigated the association between medication regimen complexity and medication adherence in patients undergoing haemodialysis. This study had a good response rate of above 75%, with 53 patients undergoing haemodialysis completing the study. These patients were re-invited for participation in the qualitative interview. Thirty patients consented and completed the qualitative interview, the non-participation of the remaining 23 patients was mainly due to lack of interest, fatigue or perceived inconvenience.

4.3.4. Data Collection and Analysis

One-to-one semi-structured interviews were held during the dialysis session. All interviews were conducted by SG between February and June 2015, using the interview guide (**Appendix 8**), and the median interview duration was 17.5 minutes (range, 6-41 minutes). All interview sessions were audio-recorded and transcribed verbatim; patients were not remunerated for their participation. Data on socio-demographic and clinical characteristics were obtained during interviews and by reviewing medical records. Adherence was determined by self-reporting using the 4-item Morisky Green Levine scale [20]. Patients with a Morisky score of zero were considered adherent and those scoring 1-4 were considered nonadherent, based on similar studies assessing self-reported adherence in patients undergoing haemodialysis [150, 229].

Interview transcripts were analysed using the template analysis method [230]. Transcripts were repeatedly read for familiarisation and data immersion. Two investigators (SG and STRZ) independently coded and reviewed the first five transcripts to ensure concordance was reached. Remaining transcripts were coded by

SG and the final themes were agreed upon by both SG and STRZ. The analysis was iterative during data collection and carried out following each interview. Data saturation was assumed after 18 interviews. However, all participants who consented for the study were interviewed. Themes generated were mapped against the World Health Organisation (WHO) determinants of medication adherence that included patient-related-, health system/ healthcare team related-, therapy-related-, condition-related-, and social/ economic related factors [16]. Patient-related factors within the WHO model were further sub-divided into such aspects as knowledge, awareness, attitude, self-efficacy, action control, and facilitation, based on an adherence support taxonomy of behaviour change techniques [231].

4.4. Results

Table 9 shows the study characteristics of the participants. The median age was 71 years (range: 44-87 years), and the patients were taking 4-19 medications daily. More than half of the participants were nonadherent to their medications, based on self-reporting measure (56.7%, n = 17).

Table 9. Characteristics of Study Participants (n = 30)

Variables	**Number (%)**
Age, in years	69.6±11.0
40-59	5 (16.7)
60-79	18 (60.0)
≥80	7 (23.3)
Gender, male	23 (76.7)
Marital status, married	17 (56.7)
Living with family	18 (60.0)
Level of education, ≥ high school	24 (80.0)
Smoking history, non-smoker	24 (80.0)
Number of medicines prescribed	11.4±4.3
1-5	4 (13.3)
6-10	7 (23.3)
≥11	19 (63.3)
Daily pill burden	16.0±6.1
1-9	4 (13.3)
10-19	15 (50.0)
≥20	11 (36.7)
Years on dialysis	4.1±4.1
<1	6 (20.0)
1-5	17 (56.7)
≥6	7 (23.3)
Hospitalisation (past one year)[ǂ]	22 (73.3)
Dialysis session missed [ǂ]	5 (16.7)
Diabetes	7 (23.3)

Variables	Number (%)
Hypertension	17 (56.7)
Cardiovascular disease	16 (53.3)
Adherence to medication [μ]	
Adherent	13 (43.3)
Nonadherent	17 (56.7)

Note: For continuous variables, Mean±SD; for categorical variables, numbers with percentages in parentheses.

[μ] Adherence to medication was based on self-reported measure using 4-item Morisky Green Levine scale. Patients scoring zero were considered adherent.

[ŧ] At least one event of hospitalisation or dialysis session missed in past one year prior to the month of data collection.

The exemplar quotes for each theme are provided in **Table 10**. A full compilation of quotations is supplied as **Appendix 9**. The major themes, classified according to WHO determinants of adherence, are presented below. Please note the following abbreviation for the section below: P = patient (with a number to indicate the interview sequence, for example, P5 is the fifth interviewed patient).

Table 10. Determinants of medication adherence in patients undergoing haemodialysis

Themes based on WHO taxonomy	Exemplar quotes
Patient-related[µ]	
Knowledge and belief about medicines	
- *Lack of understanding about medicines*	*"Well, I just don't know what some of them are for."* (P1, male, 53 years, PSR NAD) *"I don't know what's really important and… if you missed [medication] once or twice it wouldn't matter, I've no idea."* (P5, female, 58 years, PSR NAD) *"As far vitamins are no much point for me because it all gets dialysed out of here [pointing to the dialysis machine]."* (P8, male, 71 years, PSR NAD)
- *Lack of benefit*	*"I don't know if they doing any good? […] I thought well, you know, I am taking all this in the morning, um… are they doing any good? I don't know."* (P5, female, 58 years, PSR NAD)
- *Safety concerns*	*"There's one medicine that is a statin which I'm very unhappy about. It's Atorvastatin. And, I'm unhappy about that… because they… they, ah, studies have shown that there are lots of side effects of that."* (P6, female, 74 years, PSR NAD)
- *Relative importance*	*"I think blood pressure one is important. Yes, I think that is important to keep my blood pressure down…"* (P6, female, 74 years, PSR NAD)
- *Perceived need*	*"There's something to do with my kidney and that. […] it's not working very well. If I started not taking them, I could for been… you know in trouble. They all they are for a reason. Yeah."* (P15, male, 78 years, PSR AD)
- *Perceived effectiveness*	*"I put myself on that [medicine] because I didn't have any arthritis or anything before I started [dialysis] and all of a sudden my fingers going, and I put it on that now for a month and it stopped the pain…"* (P12, female, 80 years, PSR AD)
Awareness and attitude	
- *Motivation to live*	*"I don't know how much longer I got to live. But I want to get up to 80. If I become 80, that will be the longest lived in all our family. And if I make 80… I'm the champion."* (P15, male, 78 years, PSR AD)

Themes based on WHO taxonomy	Exemplar quotes
- *Positive attitude*	*"I got to take them as they keep me healthy. And I don't have a problem with it."* (P21, male, 84 years, PSR AD)
- *General dislike*	*"I don't like the fact that I need to take them… Not happy about taking medications but the alternatives not good."* (P13, female, 63 years, PSR NAD)
Self-efficacy	
- *Disruption to daily routine*	*"Well it's in the morning and night, I'm just used to doing that. It's the middle one I have to take care of… I take it at night. Take two at night instead of three, spreading three during the day, which the doctor asked me to try, because it might be more effective. I haven't yet succeeded."* (P8, male, 71 years, PSR NAD)
- *Inconvenience during travel*	*"People don't make it difficult for me, but it's the fact that I've, I travel, I like to travel of course make it difficult, because I've got to take all the stuffs with me, organise something every day or whatever. Yes, traveling."* (P6, female, 74 years, PSR NAD)
- *Accustomed regimen*	*"I got all these medications every day, morning, evening, night. So, I never forget it, now."* (P15, male, 78 years, PSR AD) *"I've been taking it for a long time and it's just natural."* (P27, male, 79 years, PSR AD)
- *Unaccustomed regimen*	*"I'm supposed to take a medicine for my [restless leg], but I keep forgetting… So, um, I've only been told this few days ago and I haven't got used to it, to taking it."* (P8, male, 71 years, PSR NAD)
Action control	
- *Forgetfulness*	*"Well, I think that I'm much more, I don't know, forgetful then I used to be, I can't think this clearly… seems I pick but I don't. Um. Remembering to take it. I think that's the biggest thing."* (P6, female, 74 years, PSR NAD)
- *Stimuli or cues for action*	*"I have a little pill boxes, it holds all morning, noon and night… I just take whatever is required during dinner, or at meal in the night."* (P15, male, 78 years, PSR AD)
- *Visual allocation of pills*	*"I've got them [medicines] in the kitchen table, so I can't forget."* (P10, female, 53 years, PSR AD)
- *Association with meals*	*"If I don't have lunch, I don't remember my medicines, always. Lunch is sort of tied to the medicines. So, if I wouldn't eat, I wouldn't take the medicines so regularly, I think."* (P6, female, 74 years, PSR NAD)

Themes based on WHO taxonomy	Exemplar quotes
Facilitation	
- *Role of support*	*"My wife makes sure I take them... she helps. She gets all medicines ready, tablets ready… she does all, mostly."* (P27, male, 79 years, PSR AD) *"Some medicines make me dizzy. It is a problem. Especially when I get no support at home. Coz my husband, he works at night, and I got to be careful. Coz I got no support at home."* (P7, female, 65 years, PSR NAD)
Health system/ HCT-related	
Quality of interaction with HCT	
- *One-way communication*	*"[Asking Dr about the need of so many medicines…] I saw doctor at the clinic last time and he said, "No, they are all good". He went through one by one [medicines] and no, that's good, you need that, you need that, so…"* (P7, female, 65 years, PSR NAD)
- *Lack of engagement*	*"[Consultations are] never very long usually, you know. Just checks the figures, just look at your blood figures and everything's ok and you know."* (P2, male, 61 years, PSR NAD)
- *Lack of time*	*"I really need to speak to the pharmacist. Um, but they're very busy, but I will, I must speak to, I want to know what every medicines, especially 12 medicines in the morning are for."* (P5, female, 58 years, PSR NAD)
- *Support from HCT*	*"It's always great with my GP. I've been going to him for 15 years and we're quite informal and he's very helpful and if I complained about what these things, he investigates them properly."* (P11, male, 84 years, PSR AD) *"You know, just, give all your tablets to the chemist and he'll sort them out. Makes it so much easier. He puts them in [Webster-Pak] … for two weeks and you got a just twist and pop a tablets… so I don't need to worry about what one of this, one of this, anymore."* (P16, male, 65 years, PSR AD)
Mistrust and collateral arrangements	
- *Pressure to hide*	*"I forgot to say [doctor] about it [not taking phosphate binders]. Because, I think what they will gonna tell me is, I have to take it. I'm frightened obvious the doctor's gonna say, which they probably will, because it's very important, the phosphate, I know that."* (P5, female, 58 years, PSR NAD)

Themes based on WHO taxonomy	Exemplar quotes
- *Being a good patient*	*"I don't. I don't know I take it because I've been told to take it, and I do that. But I don't take it very seriously. And if I miss it, I don't get panic, so."* (P8, male, 71 years, PSR NAD)
- *Personal control of treatment*	*"I discuss it with myself. Or, I go to [doctor] who gets upset because I decide to take more than what I'm prescribed. Like the Sifrol, it wasn't holding, so I lifted the [dose] up to two. And checked it [in the internet] and it was okay to do that and then she [doctor] got most upset because she said it effects the kidney, and I said well they're pretty shot already, and she said they can always get worse."* (P8, male, 71 years, PSR NAD)
- *Trust in HCT*	*"I take my medicines. They give me the right thing, so I just take them. Except when I'm allergic to."* (P10, female, 53 years, PSR AD) *"I keep taking them until my doctor takes me out of it. I just take the dose that's on the charts I got."* (P25, male, 72 years, PSR AD)
Therapy-related	
Physical characteristics of medicines	
- *Pill size*	*"I've got the one [medicine], got to cut it half, I've got a cut five or six in half so I've got half for in the morning and half at night."* (P9, female, 63 years, PSR NAD)
- *Palatability*	*"Some of them, as soon as you get them on the tongue…I swear it, dissolves straight away and it tastes disgusting! First thing in the morning they, oh! […] Just bitter, you know, one of them."* (P5, female, 58 years, PSR NAD)
Medicine packaging	*"One I have very hard to get it out. A little capsule, that for pain. Yeah. Very hard to put out. The capsules are completely crushed by the time it gets out of its thing! That's the only problem."* (P11, male, 84 years, PSR AD)
Side effects of medicines	*"Sometimes they work, sometimes really make me sick. Makes me dizzy. It's a bit stronger. I don't take them. If they are not too strong, I'll take them… but if they make me dizzy, I don't."* (P7, female, 65 years, PSR NAD) *"I don't like taking them, the [antibiotics], they give me toilet all the time."* (P29, male, 65 years, PSR NAD)
Social/ economic	
Access to medicines	

Themes based on WHO taxonomy	Exemplar quotes
- *Acquiring script*	*"I'm taking a lot of pain tablets at the moment… I was taking patches, but you can't get more than a month's supply. So, that means going back on doctors, and when I get out of here [dialysis], I don't want… to get to the doctors on my days off [from dialysis], so I'm just taking Panadol and Panadol with Codeine. But, is not really enough, to be honest."* (P2, male, 61 years, PSR NAD)
- *Clinic and pharmacy location*	*"Because I live out of town… and about 40 minutes from the chemist, just kind of be aware how many more medicines I've got, it's nothing worse than running out and having to drive especially for that, yeah."* (P3, male, 44 years, PSR NAD) *"Some of the scripts you can't get from [local pharmacy]. So, I've had issues actually getting them in the past… When my doctor goes on holidays, I can't acquire a script without doing it a 100 km drive. [Dialysis staffs] refused to help me, and the doctors refused to give scripts over the phone. I can't acquire a script over the phone…"* (P1, male, 53 years, PSR NAD)
Relative affordability	*"Well, they're quite expensive! So they do affect me, the cost. I don't have a health care card. I've to pay the full subsidised price… I've retired and so I'm living of an allocated pension from my superannuation."* (P4, male, 56 years, PSR NAD) *"The only thing that worries me is, coz I'm in a wheel chair and I need to get to the hospital to get the scripts, it means for $ 30 to get in the taxi to go in there and pick up the script or I drive my mobility scooter all the way in there, which means two hours and an hour of each waiting to pick them up."* (P2, male, 61 years, PSR NAD)
Condition-related	
Symptom severity	*"Have you seen me 12 months ago, I am on a 100 % better [condition] after this year but last year and a year before, no, I didn't really think I'm gonna make it. Not even everybody else also gonna make it either."* (P12, female, 80 years, PSR AD) *"I don't notice any [improvement] from my medications, whatsoever."* (P1, male, 53 years, PSR NAD)

Abbreviations: AD, Adherent; NAD, nonadherent; BP, blood pressure, HCT, healthcare team; PSR, patient self-reports

[μ] Patient-related factors further classified based on adherence support taxonomy by de Bruin *et al*., 2010.

4.4.1. Theme 1: Patient-related Factors

4.4.1.1. Knowledge and belief about medicines

Patients assigned varied importance to their prescribed medicines and it appeared that the patients who were less informed of the purpose of their medicines saw little reason for taking them regularly (P1, P5). This lack of understanding also led to the misconception that some of their medicines get washed out during dialysis and would become ineffective (P8). Such misconceptions triggered doubts about their necessity, which led to prioritising medication due to perceived lack of benefit (P1, P5), and relative importance given to some medicines (P6), thus encouraging nonadherence behaviour. Furthermore, some patients acquired nonadherent behaviour as they expressed safety concerns about their medications (P5, P6). On the other hand, patients having a better understanding of their disease process had higher perceived need (P11, P15, P16) and developed perceived effectiveness (P12) of their medication therapy, and were therefore adherent.

4.4.1.2. Awareness and attitude towards medicines

Being aware of the consequences of nonadherence, such as deterioration of the medical condition and, in rare cases, fear of death, was found to be a motivator to be adherent. Motivated patients desiring to live longer (P12, P15, P20, P21, P25) and those expressing positive attitude towards taking medicines (P10, P11, P15, P21, P24, P28) were thus found to be adherent. On the contrary, a patient who was not motivated to overcome a general dislike of taking medicine was likely to demonstrate a nonadherent behaviour (P13).

4.4.1.3. Self-efficacy

Patients' ability to manage their medication in different situations also influenced their medication-taking behaviour. Disruption to daily routine, particularly the midday dosing frequency, was identified as a practical barrier to medication adherence. This was pertinent in patients expressing personal preferences for taking medications at their convenience (P8) or in those prioritising important life events of the day over taking medicines (P18). Also, some participants accentuated that carrying medicines and remembering to take them was inconvenient during their travel and outdoor activities (P3, P6). Patients accustomed to their regimen, after following a routine for a relatively longer span of time, were found to be adherent (P15, P16, P20, P21, P27, P30), whereas a patient who was unaccustomed to recent changes in his medication regimen had a tendency to forget and was more likely to be nonadherent (P8).

4.4.1.4. Action control

Patients' capacity to control medication intake as planned was also influencing medication adherence. Participants expressed forgetfulness as an excuse for not taking medication and gave an impression that nonadherence was unintentional (P6, P8, P14). Adherent patients, however, made their circumstances favourable for taking medicines by using stimuli such as pill boxes (P15, P18, P25) or by visibly allocating their pills (P10, P12). Furthermore, some patients connected their meals and medicines together by stating that skipping meals during the day might result in their not taking their medicines (P5, P6).

4.4.1.5. Facilitation

Patients who were influenced and reinforced by their family members (P12, P15, P21, P27) were better at adhering to their medication regimen, whereas patients expressing lack of support from their family members (P7) or those who lived alone (P2) were found to be nonadherent to their medications.

4.4.2. Theme 2: Health System/Healthcare Team-related Factors

4.4.2.1. Quality of interaction with healthcare team

A few patients expressed dissatisfaction with their interaction and engagement with the healthcare team and were likely to demonstrate nonadherent behaviour. Some of the issues raised by these patients include one-sided communication with their physician (P7), non-concordance during consultation visits (P2, P4); and a perceived lack of time for medication counselling (P5). Some patients avoided discussing adherence related issues with their doctors as they had a preconceived notion about what their doctors would say. This might have occurred due to previous unpleasant interactions with their doctors. For instance, a participant remembered an occasion when the doctor showed less empathy towards her unresolved symptoms, despite her taking medications (P5). On the other hand, patients expressing satisfaction with their interaction and engagement with the healthcare professionals tended to be adherent to their medications (P11, P16).

4.4.2.2. Mistrust and collateral arrangements

A general lack of trust in the healthcare team, particularly in the medical profession was reported by some patients. Those who perceived that their concerns about medications would not be attended to by their doctors preferred either hiding their concerns (P5) or portraying themselves as good patients (P6, P8). Dissatisfaction and mistrust, as a result of unpleasant interactions with physicians, may have further aggravated patients into making parallel or collateral arrangements for themselves, by surpassing the physicians' decisions and recommendations regarding their medications. In this way, patients felt that they had exerted a sense of personal control over their treatment (P2, P7, P8). In contrast, patients who were experiencing a satisfactory and trusting relationship with their doctors seemed to have followed the prescribed instructions in a relatively compliant fashion (P10, P11, P15, P20, P25).

4.4.3. Theme 3: Therapy-related Factors

4.4.3.1. Physical characteristics of medicines

Physical characteristics of medicines were considered to hinder adherence in some patients. For example, pharmaceutical characteristics such as the size of pills, especially the larger ones (for example, phosphate binders) which were considered difficult to swallow (P9, P10). In addition, a few patients complained about palatability of medicines to be a problem when they had to be taken early in the morning (P5, P13, P22).

4.4.3.2. Side effects of medicines

Some patients complained about side effects such as dizziness, nausea, vomiting and diarrhoea after taking their medicines (P5, P7, P29). They experimented on their own by skipping doses and observing if the symptoms persisted. When patients were convinced that their past experiences of untoward symptoms were the results of taking their medicines (P5, P7, P29), they would prefer to avoid those medicines to ensure that they would not suffer from similar adverse effects in the future.

4.4.3.3. Packaging of medicines

One patient considered one of his medicine packaging to be non-user-friendly (P11), posing it to be a practical barrier that impeded adherence.

4.4.4. Theme 4: Social/Economic Factors

4.4.4.1. Access to medicine

Medicines in Australia are supplied at a subsidised cost through the Pharmaceutical Benefits Scheme (PBS). However, access to some specialised medicines routinely used in patients undergoing dialysis (such as Lanthanum, Erythropoietin, Cinacalcet and so on) is restricted to specialised pharmacies and hospital based clinicians. This becomes an issue particularly for patients who are living far away from the major town or cities and requiring scripts; in their local areas they are offered only limited access to professional medical services (P1, P3). In addition, under the PBS, patients are constrained to filling their prescription to no more than a month's supply, which makes frequent visits to acquire scripts inconvenient for patients having dialysis fatigue and

chronic incapacitation (P2, P23). This results in medicine shortage and patients are compelled to choose readily available over-the-counter medicines that may not always be effective alternatives (P2). Besides acquiring scripts, the clinic and pharmacy locations also posed a limitation for accessing medicines for patients living in remote areas (P1, P3).

4.4.4.2. Relative affordability

The relative affordability of medicines due to cost or financial constraints was another factor that impedes access to medicines and ultimately contributed to nonadherence. Some of the patients undergoing haemodialysis were over the retirement age and lived on disability support pensions, superannuation or disability benefits (P2, P4). Although patients were getting medicines with a highly subsidised price through the PBS, this tends to cover only a partial cost of prescription medicines. However, due to the complexity of disease treatment and associated symptom burden, patients often required additional over-the-counter medicines, including multi-vitamin preparations, vitamin D, iron and mineral supplements, pain medicines and so on. These medicines are not covered by the PBS and patients needed to pay for them out-of-pocket. The relative affordability of these medicines, when considering the cost of acquiring scripts, transportation costs to visit a health service facility and medicine costs, restrained patients from accessing their medicines (P2, P4, P5).

4.4.5. Theme 5: Condition-related Factors

4.4.5.1. Symptom severity

Severity of symptoms had an influence on patients' risk perception, importance of following treatment regimen and the priority they placed on medication adherence. A patient who observed decreased symptom severity over time was found to be adherent with her prescribed regimen (P12). However, another patient who did not see any improvement of his health condition was found to be nonadherent (P1).

4.5. Discussion

This qualitative study explored factors associated with medication adherence in patients undergoing haemodialysis, and examined their perceptions on medication-taking behaviour. A dissonance of perceptions with respect to adherence behaviour was observed between adherent and nonadherent patients. Most factors influencing medication-taking behaviour were patient-related. Some of the factors identified corroborated with past findings such as safety concerns of medicines [225, 226, 232], disruption to daily routine [226], forgetfulness [225, 232], use of reminders [226, 228], and the role of social support [150, 228].

Knowledge and beliefs about medicines were essential patient-specific factors, potentially impeding adherence behaviour. Patients prioritised their medicines due to poor understanding about medicines, perceived necessity and concerns regarding medicines, all of which resulted in nonadherence behaviour. These findings in relation to patients' beliefs regarding their medication can be further studied through various behavioural models of adherence (for example the Medication Adherence Model, the Health Belief Model, the Theory of Planned Behaviour) [233-235]. Belief components, such as necessity and concerns, can be specifically targeted by utilising tools such as

the Beliefs about Medicines Questionnaires (BMQ), particularly the Specific-Necessity and Specific-Concerns scale [236]. Patients' beliefs about necessity and concerns related to medicine can be overcome through psycho-educational interventions [237]. Thus, our study re-emphasises the need for providing medication-related information to combat patient ignorance about medications in those undergoing haemodialysis [226, 238].

Patients reporting poor interaction with healthcare providers displayed a compromised adherence behaviour. In particular, patients were less satisfied with the consultations that lacked inquiry about their experiences of taking medicines and any adverse effects they might be suffering. Although patients reporting medication-related symptoms to their physician is less frequent, physicians do not necessarily always respond to them, even if they were reported [239, 240]. Suboptimal patient-physician interaction may lead to patients losing trust with physicians' recommendations and hiding their concerns, while trying to be a good patient [225]. This may also lead to patients making collateral arrangements for their medications to exert a flawed sense of control over their treatment, resulting in nonadherence. Thus, it is extremely important for the healthcare professionals to routinely instigate dialogues about medication issues with patients and encourage them to volunteer such information if they were not being asked for it during consultations [239].

Socio-economic factors, such as access to medicine and its affordability, also raised concerns that hindered adherence. Access to prescribed medicines and professional medical services gradually decline when moving away from metropolitan cities through to rural and remote locations [241]. Although our study site was located in the metropolitan city, some patients visiting the dialysis centre lived in rural areas and were required to travel to the city where they could access professional advice for

acquiring prescriptions or repeating them at the pharmacy. Though eligible patients benefitted from the government subsidy schemes for cost reductions in prescription medicines [242], the large financial burden accumulated from the number of prescription and non-prescription medicines, the cost of acquiring scripts, transportation, and out-of-pocket payments annulled the cost benefits from the subsidy for patients undergoing haemodialysis. Medicine affordability can be much more challenging for patients in developing countries where a public healthcare system does not guarantee subsidy of prescription medicines and patients generally do not subscribe to health coverage schemes [243].

This study finding has both clinical and research implications. As dialysis patients, coupled with comorbid illness and dialysis-associated complications, continually demand a high pill burden for treatment, we tend to lose sight of how polypharmacy, regimen complexity and adherence issues should be addressed. As such, this study provides a subjective account of patients' concerns that may lead to nonadherence. Healthcare professionals could routinely instigate dialogues with patients and encourage them to volunteer information concerning their current medicines, their readiness to start new therapy, any changes with dose or dosage requirements and any side-effects or safety concerns with which they might be dealing. Any transitioning of medication therapy could be facilitated by providing personalised education, capitalising on the need for and importance of taking medicines. Improving access to professional medical and pharmaceutical services, developing dialysis centre-based intervention programs and focussing on psycho-educational support could be effective. The same framework could be utilised in research settings to develop behavioural and educational interventions for examining patient concerns associated with medication adherence.

Study limitations require a mention. This is a single-centred study that could limit the generalisability of the findings. Interviews were conducted with English speaking patients only, thus, the findings may not be generalisable to non-English speaking patients. Although the participants were interviewed in an outpatient setting in a tertiary care metropolitan hospital, some of the patients came from rural areas, necessitated by access limited healthcare services and support mechanisms. Hence, the access barrier gained attention in our themes, which might only be true for patients living in rural areas [232]. As interviews were conducted during dialysis sessions, patients could have been hesitant in responding freely while sharing their experiences. Furthermore, interviews for research purposes could have facilitated a social desirability response [244], although it was unlikely as wide-ranging viewpoints were expressed. Despite limitations, we used a purposive sampling method to identify participants of different demographic characteristics, showing different medication-taking behaviour that best represented the perspectives of patients regarding the phenomenon under study.

4.6. Conclusions

Patients undergoing haemodialysis expressed a number of concerns that led to nonadherence behaviour. Many of the issues identified were patient-related and potentially modifiable by using psycho-educational or cognitive-behavioural interventions. Healthcare professionals should be more vigilant towards identifying these concerns to address adherence issues. Future research should be aimed at understanding healthcare professionals' perceptions and practices of assessing medication adherence in patients undergoing dialysis. This could guide intervention to resolve this significant issue of medication nonadherence.

Supporting Information

Appendix 7. COREQ Checklist.

Appendix 8. Interview Guide.

Appendix 9. Full compilation of exemplar quotes.

CHAPTER FIVE

5. RENAL PHARMACISTS' PERCEPTIONS AND CURRENT PRACTICES OF ASSESSING MEDICATION ADHERENCE IN DIALYSIS PATIENTS: DEVELOPMENT AND PILOTING OF A SURVEY TOOL

5.1. Abstract

Background: Medication nonadherence is a major problem in chronic kidney failure patients undergoing dialysis. Pharmacists play a vital role in improving medication-related patient outcomes, reducing drug-related problems, and improving medication adherence. However, little is known about the current practices of pharmacists in assessing adherence in patients undergoing dialysis.

Objective: To develop and pilot a survey instrument to measure pharmacists' perceptions, current practices, and barriers to assessing medication adherence in patients undergoing dialysis.

Methods and materials: Specialist renal pharmacists in Australia were surveyed during March and May 2016. The survey included five psychometric scales measuring perceived prevalence and contributors of nonadherence, effectiveness of methods, barriers and confidence to assess adherence on a 10-point Likert scale (1 = strongly disagree, to 10 = strongly agree). Current adherence assessment practices were identified using a 4-point graded response (1 = do not practise at all, to 4 = practise for every patient).

Results: The survey tool demonstrated an acceptable overall reliability with a Cronbach's alpha of 0.79. A total of 41 pharmacists completed the survey (response

rate, 91.1%); a majority (91.9%, n = 34; median = 8.0) believed that patients were nonadherent to their medication. Objective blood monitoring was most frequently used to determine nonadherence (57.1%, n = 16); subjective patient interviews were rarely conducted (27.6%, n = 8). Time constraints (43.8%, n = 14) and lack of administrative support (31.3%, n = 10) were perceived as barriers to assessing adherence. Although all pharmacists (100%, n = 33) support the presence of dedicated pharmacists for assessing adherence, only 24.2% were actually performing this function.

Conclusions: Pharmacists were rarely assigned to assess adherence in dialysis settings. Established self-reporting methods to measure adherence were under-utilised compared with objective blood monitoring. Having renal-specialised pharmacists in dialysis centres might facilitate adherence promotion and early identification of medication-related issues in patients undergoing dialysis.

Keywords: Adherence assessment practices; cross-sectional studies; dialysis; kidney failure, chronic; medication adherence; pharmacists

5.2. Impact of Findings on Practice

- Medication nonadherence in chronically ill patients is a major determinant of poor patient outcomes.
- Dialysis centres routinely rely on blood results to detect medication nonadherence, with little to no attention being paid to patient engagement via self-reporting measures.
- Renal pharmacists are highly confident in their ability to identify and resolve medication-related issues in patients undergoing dialysis.
- Having dedicated renal pharmacists in dialysis centres would facilitate assessment and promotion of medication adherence in patients undergoing dialysis.

5.3. Introduction

Medication nonadherence is a global problem of striking magnitude [16]. An estimated 50% of patients with chronic diseases do not take their medicines as prescribed [16]. Poor patient adherence has led to increased morbidity and mortality in patients, incurring an annual direct expenditure of approximately $100 billion [2]. The vast majority of clinical research has been focussed on improving patient outcomes from medication therapy [1]. Yet, little emphasis is given in validating whether or not patients are actually adhering to their prescribed regimen. Not that adherence is not measured in routine settings; various objective and subjective tools have been designed to measures adherence [2]. However, in clinical practices, the use of proxy measures, such as objective blood monitoring for drugs, physical assessment and monitoring vitals, observing clinical responses or side effects from therapy, checking pills and so

on, are more common [2, 33]. Assessment from these methods could give skewed results as they do not tend to truly reflect on the medication-taking behaviour of the patients. Similarly, self-reporting methods, although prone to social desirability responses [229], can be effective means to get closer to the patients and better understand their concerns, as related to medicines. However, identifying patients' medication-taking behaviour can be a challenging endeavour in routine clinical practice [1]. Lack of time, increased work pressure and other clinical priorities may not allow healthcare professionals to spend a dedicated amount of time to discuss medication-related problems with patients [232]. On the other hand, end-stage kidney disease (ESKD) patients undergoing chronic dialysis are unique patient cohorts who provide an opportunity to frequently interact with the healthcare professionals, usually three times a week for a period of three to five hours a day. Such an engagement provides an excellent opportunity for the renal healthcare professionals to educate and encourage medication adherence in patients undergoing dialysis.

Medication nonadherence is a major problem in ESKD patients receiving dialysis and they have the highest daily pill burden compared with patients who have chronic cardiovascular diseases or HIV [10]. The median pill burden in patients undergoing dialysis has been reported as high as 19 pills per day, with a quarter of them taking more than 25 medications daily [9]. Such high pill burden may have resulted from the increased burden of concomitant illness and dialysis-associated complications, leading to an increased complexity of various treatment regimens [229]. Overall, half of the dialysis-treated patients are nonadherent to at least part of their dialysis regimen, with medication nonadherence ranging between 12.5% and 98.6% [23, 139]. The deterioration of the underlying disease conditions in patients undergoing dialysis following nonadherence has been associated with increased mortality and

recurrent hospitalisations, incurring a substantial economic burden on the healthcare system [23].

Healthcare professionals, including pharmacists, strive for the selection of best possible medications for their patients. Pharmacists are well positioned to optimise medication therapy, identify impediments to adherence and develop methods to address and educate patients, as well as the allied healthcare team, on medication-related issues [245]. Pharmacists' involvement has significantly reduced hospitalisation rates and cumulative time spent in hospitals in patients undergoing dialysis [246], with trends towards a reduction in all-cause mortality [247]. Furthermore, pharmacist implemented protocols have improved the phosphate and anaemia management in patients undergoing dialysis [248, 249]. However, there is insufficient evidence as to the extent of pharmacists' awareness of adherence assessment practices and of how much time is devoted to assess and promote adherence in dialysis settings. To implement adherence assessment practices in routine patient care, it is imperative to understand how pharmacists perceive the issue of nonadherence in patients undergoing dialysis. No prior studies have attempted to study current practices and barriers faced by renal pharmacists while measuring and promoting medication adherence in patients undergoing dialysis.

5.4. Aim of the Study

To develop a survey tool and understand renal pharmacists' perceptions, current practices, and barriers to assessing medication adherence in patients undergoing dialysis.

5.5. Ethics Approval

Approved by the Tasmanian Social Sciences Human Research Ethics Committee, University of Tasmania (H0015433).

5.6. Method

5.6.1. Study Design

A cross-sectional survey design was used. We followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline (**Appendix 10**) for the conduct and reporting of this study [14].

5.6.2. Setting and Recruitment of Participants

All renal-specialised pharmacists currently registered to practise in Australian dialysis centres were eligible to participate. Recruiting participants directly was not feasible due to the lack of an assured means of identifying pharmacists involved in the care of patients undergoing dialysis; thus we sought recruitment through a professional renal forum, The Australasian Renal Pharmacists (ARP), a renal-specialised pharmacists' discussion forum, associated with The Society of Hospital Pharmacists of Australia (SHPA). The ARP consisted of 45 active members during the time of data collection.

5.6.3. Data Collection

The survey was hosted online for a period of 12 weeks between March and May 2016. During this period, an invitation flyer describing the study aims and a hyperlink to the online survey were circulated to participants on a fortnightly basis through email alerts,

e-newsletters, and social media posts, in cooperation with the SHPA. Survey completion was followed by a lucky draw to randomly select eight participants to receive gratitude gift vouchers worth AUD $100 each for participation.

5.6.4. Survey Development

Survey instruments that measured pharmacists' perceptions and practices of assessing medication adherence in patients undergoing dialysis could not be identified. Hence, we designed a survey tool following an extensive literature review [23, 111, 250-253], applying the basic principles of survey research [254, 255]. Initially, 82 survey items were generated within the themes: perceived prevalence and contributors of nonadherence, barriers to measuring adherence, confidence in assessing adherence, and effective measures of identifying nonadherence. Following content review, five items were removed due to duplication and relevance. Following this, expert consultants (a nephrologists, two renal nurses and a pharmacist) were sought to review the questionnaire. Following suggestions, five more items were removed, limiting the questionnaire to 72 items. For the face and content validity, readability and comprehensiveness of the questionnaire, a convenient sample of ten renal healthcare professionals (five renal nurses, three renal pharmacists and 2 nephrologists) were invited to complete the survey and feedback was requested about the completion time, ease of completion and clarity of the questionnaire. This step led to a further deletion of 15 more items from the instrument.

The final instrument was comprised of 57 items, subdivided into seven sections. The first section contained 14 questions about study demographics. The following five sections sought to understand participants' perceptions on the prevalence of

medication nonadherence (ten questions), contributors of nonadherence (ten questions), perceived effectiveness of methods to identify nonadherence (six questions), barriers to assessing adherence (six questions), and participants' confidence in assessing adherence (five questions). Participants' perceptions were measured on a 10-point Likert scale of agreement, where 1 = strongly disagree and 10 = strongly agree. The final section, contained six questions that surveyed current practices of assessing adherence through a 4-point graded response, including practice for some patients (with a higher risk of adverse effects), for most patients (routine practice except for lower risk patients), practice for every patient, and not applicable (do not practice at all). The survey questionnaire was also intended for administration to other renal healthcare professionals besides pharmacists. Hence, the demographic information section of the questionnaire is also capable of capturing professional designation for other renal healthcare professionals, including renal nurses and physicians. The survey questionnaire is supplied as **Appendix 11**.

5.6.5. Statistical Analysis

Data were analysed using SPSS version 23.0 (IBM Corp., USA). Descriptive analysis was performed to describe demographic characteristics and frequency rates. Normality of data was tested using the Kolmogorov-Smirnov and Shapiro-Wilks tests. The Median with Inter Quartile Range (IQR) was used to summarise continuous variables. For non-normally distributed data, the Mann-Whitney or Kruskal-Wallis tests was performed to detect the differences in median scores. A post-hoc analysis, using the Dunn-Bonferroni test, was employed to identify statistically significant differences between intergroup variables [256]. A p value of < 0.05 was considered statistically significant.

5.7. Results

A total of 41 renal pharmacists completed the survey, with a response rate of 91.1%. The majority of the participants was females (68.3%, n = 28), and aged between 31-40 years (51.2%, n = 21). The study characteristics of respondents are presented in **Table 11**.

5.7.1. Reliability of Scales

The internal consistency and reliability of perception scales was measured using Cronbach's alpha coefficient. The overall reliability, comprising all five scales, demonstrated an acceptable level of internal consistency, with an alpha of 0.79. The reliability coefficient for each scales was as follows: perceived prevalence scale (0.91), perceived contributors (0.74), perceived effectiveness (0.60), perceived barriers (0.50), and participants' confidence (0.93). The details of the Inter-Item Correlation Matrix and Cronbach's alpha coefficients for each scale are included as **Appendix 12**.

Table 11. Demographics of survey respondents (n = 41)

Variable	Category	Number (%)
Age, Years		35 (range, 25-59)
	20-30	12 (29.3)
	31-40	21 (51.2)
	≥ 41	8 (19.5)
Gender		
	Male	13 (31.7)
	Female	28 (68.3)
Level of education		
	Bachelors	13 (31.7)
	Graduate certificate	17 (41.5)
	Masters and doctorate	11 (26.8)
Experience in renal unit, Years		4 (range, 1-27)
	1-5	30 (73.2)
	≥ 6	11 (26.8)
Australian State/ territory		
	New South Wales	11 (26.8)
	Queensland	11 (26.8)
	Victoria	9 (22.0)
	Western Australia	5 (12.2)
	Other territory	5 (12.2)
Organisation type		
	Public	38 (92.7)
	Private	3 (7.3)
Dialysis unit location		
	Metropolitan	31 (75.6)
	Rural	10 (24.4)
Characteristics of dialysis unit		
	Number of dialysis chairs (n = 27)	15 (range, 3-30)
	Presence of nursing educator, Yes	32 (78.0), 1.0 FTE (range, 0.5-1.0)
	Presence of pharmacist, Yes	29 (70.7), 1.0 FTE (range, 0.6-1.0)
	In-centre haemodialysis (HD)	20 (48.8)

Variable	Category	Number (%)
	Peritoneal dialysis service (PD)	1 (2.4)
	All services (HD, Home HD, PD)	20 (48.8)

Note: For continuous variables, Median (Range); for categorical variables, numbers with percentage in parentheses; *Abbreviation:* FTE, full-time equivalent of service

5.7.2. Perceived Prevalence and Contributors of Nonadherence

The majority of renal pharmacists believed that patients undergoing dialysis often forget to take their medicines (median = 8.0), changed the dosage schedule according to their lifestyles (median = 7.0), have limited understanding of their medicines (median = 7.0), were often confused and could not answer questions about their medicines (median = 7.0). The majority of the participants perceived that patients having limited understanding of their disease (median = 9.0), being prescribed with complex medication regimens (median = 9.0), lacking family or social support (median = 7.0), having a different language or cultural background (median = 8.0), and financial constraints (median = 8.0) contributed to medication nonadherence in patients undergoing dialysis (**Table 12**).

Table 12. Perceived prevalence and contributors of nonadherence in patients undergoing dialysis

Statements for	Participant's response, n (%)		Median (IQR)
Perceived prevalence	**Scoring ≤ 5**	**Scoring ≥ 6**	
Have limited understanding of their medications (n = 37)	8 (21.6)	29 (78.4)	7.0 (6.0-8.0)
Rarely ask questions about medications (n = 36)	10 (27.8)	26 (72.2)	7.0 (5.0-8.0)
Do not take their medications as prescribed (n = 37)	12 (32.4)	25 (67.6)	7.0 (5.0-8.0)
Stop taking some medications when feel better (n = 37)	15 (40.5)	22 (59.5)	6.0 (5.0-7.0)
Are often confused about medicines (n = 37)	9 (24.3)	28 (75.7)	7.0 (5.5-8.0)
Change dose/dosing interval that suits lifestyles (n = 37)	7 (18.9)	30 (81.1)	7.0 (6.0-8.0)
Express difficulty in swallowing larger pills (n = 37)	11 (29.7)	26 (70.3)	7.0 (5.0-8.0)
Don't believe current medicines are helping them (n = 37)	15 (40.5)	22 (59.5)	6.0 (5.0-8.0)
Can't answer questions about current medications (n = 37)	9 (24.3)	28 (75.7)	7.0 (5.5-8.0)
Forget to take medications sometimes (n = 37)	3 (8.1)	34 (91.9)	8.0 (7.0-9.0)
Perceived contributors	**Scoring ≤ 5**	**Scoring ≥ 6**	
Older patients are more nonadherent (n = 34)	27 (79.4)	7 (20.6)	3.0 (3.0-5.0)
Male patients are more nonadherent (n = 33)	23 (69.7)	10 (30.3)	5.0 (3.0-6.0)
Patients with multiple co-morbidities (n = 34)	6 (17.6)	28 (82.4)	6 (6.0-8.0)
Patients lacking family/social support (n = 34)	1 (2.9)	33 (97.1)	8.0 (7.0-9.0)
Patients having low income (n = 34)	5 (14.7)	29 (85.3)	8.0 (7.0-8.25)
Patients having low level education background (n = 34)	8 (23.5)	26 (76.5)	7.0 (5.75-8.25)
Having different language/cultural background (n = 33)	4 (12.1)	29 (87.9)	8 (7.0-8.5)
Having limited understanding of disease state (n = 34)	1 (2.9)	33 (97.1)	9.0 (7.0-10.0)
Patients not satisfied with their treatment/care (n = 34)	9 (26.5)	25 (73.5)	7.0 (5.0-9.0)
Patients with complex medication regimens (n = 34)	2 (5.9)	32 (94.1)	9.0 (8.0-9.0)

Note: Perception measured on a scale of 1-10, Where 1 = strongly disagree and 10 = strongly agree;
Abbreviation: IQR, Inter-quartile range.

5.7.3. Perceived Effectiveness and Barriers to Assessing Adherence

Participants unanimously agreed that having a pharmacist to conduct medication reviews and reconciliation (median = 9.0), or having a dedicated professional taking their medication history (median = 8.0), can be effective in assessing adherence. High median ratings were also observed for effectiveness of subjective methods of conducting medication history interviews (median = 8.0) and of objective methods to assess adherence through blood monitoring or physical assessment, such as blood pressure monitoring (median = 8.0).

Pharmacists unanimously disagreed about lacking knowledge and skills to assess adherence (median = 1.0). However, nearly half of them perceived that they lack time to undertake adherence promoting activities (median = 5.0). Furthermore, over a quarter of participants reported that there is no support from administration in conducting adherence promoting activities (median = 5.0). Nearly all the participants disagreed that patients would be disinterested in discussing medication-related issues with the pharmacists (median = 2.0) (**Table 13**).

5.7.4. Participants' Confidence in Assessing Adherence

Renal pharmacists were highly confident about their ability to conduct adherence assessment activities. These include the ability to conduct a medication history interview (median = 10.0), to provide medication counselling (median = 10.0), to clarify patients' medication queries (median = 10.0), to suggest strategies to improve adherence (median = 10.0), and to assess patients' knowledge and beliefs about medicines (median = 10.0) (**Table 13**).

Table 13. Perceived effectiveness, barriers and confidence to assessing adherence in patients undergoing dialysis

Statements	Participant's response, n (%)		Median (IQR)
Perceived effectiveness	**Scoring ≤ 5**	**Scoring ≥ 6**	
Interviewing patients to obtain medication history (n = 33)	0 (0.0)	33 (100.0)	8.0 (7.0-9.0)
Asking patient's family/carer about medication (n = 33)	4 (12.1)	29 (87.9)	7.0 (6.5-8.0)
Measuring objective indicators such as SPL/BP (n = 33)	3 (9.1)	30 (90.9)	8.0 (7.0-8.0)
Asking patients to bring medications and count (n = 33)	7 (21.2)	26 (78.8)	7.0 (6.0-8.0)
Having a dedicated professional to take medication history (n = 33)	1 (3.0)	32 (97.0)	8.0 (8.0-9.0)
Conducting medication reviews and reconciliation by Pharmacist (n = 33)	0 (0.0)	33 (100.0)	9.0 (8.5-10.0)
Perceived barriers	**Scoring ≤ 5**	**Scoring ≥ 6**	
Lack of knowledge and skills to assess nonadherence (n = 32)	32 (100.0)	0 (0.0)	1.0 (1.0-2.75)
Lack of time (n = 32)	18 (56.3)	14 (43.8)	5.0 (2.25-7.0)
Not my role (n = 32)	32 (100.0)	0 (0.0)	1.0 (1.0-2.0)
Patient's disinterest on discussing medication issues (n = 32)	31 (96.9)	1 (3.1)	2.0 (1.0-3.75)
No support from hospital administration (n = 32)	22 (68.8)	10 (31.3)	5.0 (2.25-6.0)
Never thought about adherence before this survey (n = 32)	32 (100.0)	0 (0.0)	1.0 (1.0- 1.0)
Participants' confidence			
Ability to conduct a medication history interview (n = 32)	0 (0.0)	32 (100.0)	10.0 (9.0-10.0)
Ability to provide medication counselling (n = 32)	0 (0.0)	32 (100.0)	10.0 (9.0-10.0)
Ability to clarify patient's medication queries (n = 32)	0 (0.0)	32 (100.0)	10.0 (9.0-10.0)
Ability to suggest strategies to improve adherence (n = 32)	0 (0.0)	32 (100.0)	10.0 (8.0-10.0)
Ability to assess patient's knowledge and beliefs about medications (n = 32)	0 (0.0)	32 (100.0)	10.0 (8.0-10.0)

Note: Perception measured on a scale of 1-10, Where 1 = strongly disagree and 10 = strongly agree;

Abbreviation*:* IQR, Inter quartile range; SPL, serum phosphate levels; BP, blood pressure.

5.7.5. Differences in Perceptions based on Study Demographics

Male pharmacists perceived fewer barriers compared with the experience of females (U = 183.0, z = 2.55, p = 0.01; male = 1.0 vs female = 2.0). Similarly pharmacists' experience in renal units significantly affected their median perceived effectiveness scores (U = 177.0, z = 2.19, p = 0.03). Compared with pharmacists working for ≥ 6 years, pharmacists with one to five years of experience perceived that current methods to assess adherence were less effective (median: 7.75 vs 8.5, $p < 0.05$). No significant differences in perceptions were observed based on age or level of education (**Table 14**).

Table 14. Differences in perceptions based on study demographics across all scales

Variables	Perceived prevalence		Perceived contributors		Perceived effectiveness		Perceived barriers		Participants' confidence	
	Median	Mean Rank	Median	Mean Rank	Median	Mean Rank	Median	Mean Rank	Median	Mean Rank
Age, years [a]										
20-30	5.5	13.4	7.0	16.9	8.0	14.5	1.5	16.0	10.0	16.6
31-40	7.0	19.7	7.0	15.0	8.0	15.6	1.5	16.2	10.0	15.7
≥ 41	7.0	25.0	8.0	25.1	8.5	23.2	2.0	18.2	10.0	19.1
Gender [b]										
Male	7.25	11.3	7.5	16.6	8.0	18.9	1.0	11.3*	10.0	19.5
Female	6.75	19.7	7.75	18.0	7.5	15.9	2.0	19.7	10.0	14.7
Level of education [a]										
Bachelors	6.0	16.3	7.5	19.7	8.0	16.8	1.5	17.8	10.0	14.4
Graduate certificate	7.0	23.2	8.0	20.2	8.5	20.9	1.5	16.4	10.0	17.3
Masters and doctorate	6.75	15.3	6.75	11.6	7.0	11.7	1.5	15.5	10.0	17.4
Experience in renal unit, Years [b]										
1-5	6.5	16.9	7.0	16.2	7.75	14.5*	1.25	15.4	10.0	15.7
≥ 6	7.0	23.9	8.0	20.3	8.5	22.1	2.0	19.0	10.0	18.2
Dialysis unit location [b]										
Metropolitan	7.0	19.4	7.5	16.9	8.0	18.0	1.5	16.4	10.0	16.3
Rural	7.0	17.8	8.0	19.6	7.0	13.1	2.0	17.0	10.0	17.2

Note: Perception measured on a scale of 1-10, where 1 = strongly disagree and 10 = strongly agree

[a] Kruskal-Wallis Test. [b] Mann-Whitney Test.

* $P < 0.05$

5.7.6. Current Adherence Assessment Practices

Figure 12 illustrates current practices of assessing adherence in dialysis centres. The majority of the participants reported that pharmacists were asked for medication reviews and reconciliation only for high-risk patients (37.9 %, n = 11). Nearly half the time dedicated professionals were not assigned to participate in a medication history interview (41.4%, n = 12). As such, medication history interviews to assess adherence were rarely conducted for every patient (27.6%, n = 8). However, assessing adherence objectively through blood monitoring or physical assessment was routinely conducted in every patient (57.1%, n = 16). Asking a patient's family or carer about medications (10.3%, n = 3) or asking patients to bring their medication and counting them was rarely practised (3.4%, n = 1).

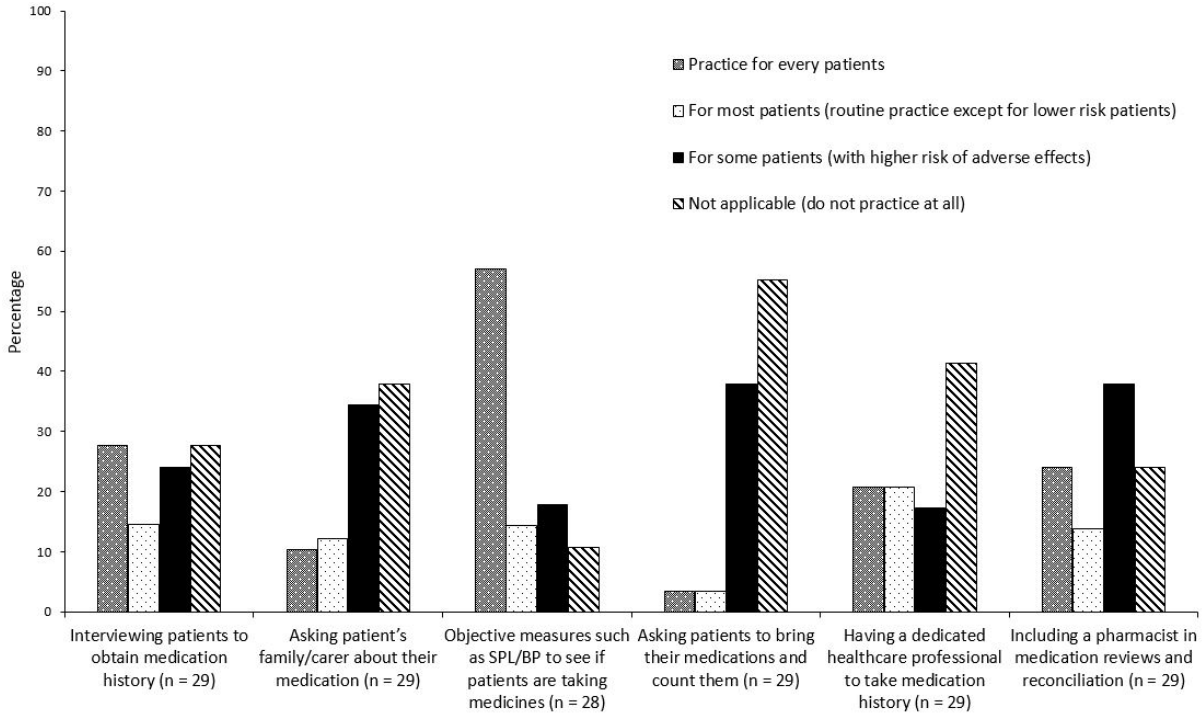

Figure 12. Pharmacists' reports on current practices of assessing medication adherence in patients undergoing dialysis in Australia

5.7.7. Qualitative Comments

Participants' comments strengthened the survey findings about contributors to nonadherence. Some of the recurring themes include knowledge and understanding of medicines, communication barriers, forgetfulness, the role of support, and the relative affordability of medicines. Participants also emphasised a substantial need for a designated renal pharmacist in dialysis settings, in order to assess medication-related issues in patients undergoing dialysis. Participants' comments are provided as **Appendix 13**.

5.8. Discussion

We developed and administered a survey questionnaire to measure pharmacists' perceptions and practices for assessing medication adherence in dialysis settings. The survey tool demonstrated an acceptable overall reliability. The study findings shows that current adherence measurement practices in dialysis settings were very limited and the established methods to screen medication nonadherence were utilised less in dialysis settings. Although renal pharmacists were highly confident in conducting adherence assessment activities, time constraints and support from administration presented as barriers to assessing adherence. Pharmacists firmly believed that having a dedicated professional or a renal-specialised pharmacist in dialysis settings would be effective in promoting adherence activities, as these services were mostly unavailable in current dialysis settings.

As medication nonadherence is highly prevalent among patients undergoing dialysis [23], renal pharmacists can play a significant role in early detection of the

underlying medication-related issues, through activities such as medication reviews and medication history interviews [257]. When reasons behind nonadherence have been identified, pharmacists can actively support the patient to achieve better therapeutic outcomes through medication counselling, education and enhancing memory through reminder calls, texts or emails, and arranging provisions such as dosage administration aids [258]. Pharmacists in this survey recognised various factors that may impede medication-taking behaviour in patients undergoing dialysis. Pharmacists' perceptions resonated well with earlier findings that patient-related factors such as lack of knowledge and understanding about medicines, lack of family or social support, forgetfulness, multiple illnesses, increased pill burden, relative affordability, and culture and communication barriers can influence medication-taking behaviour [141, 226, 228, 252]. Having a trustworthy patient-provider relationship can have a significant impact on a patient's medication-taking behaviour [225]. Patients become candid about discussing their medications with their healthcare professionals only when they feel free to admit their difficulties regarding medicines, when there is no risk of criticism and when there is a true patient-provider partnerships or concordance [259]. Renal pharmacists are well positioned in their roles to routinely instigate discussions on medication-related issues with the patients. Pharmacists can actively contribute towards designing tailored interventions that can be suitably incorporated during dialysis sessions, such as educating patients on problem solving, guiding behavioural change and taking actions in response to deteriorating signs and symptoms; all of these activities can help facilitate medication self-management in patients undergoing dialysis and improve adherence [226].

Implementing adherence assessment practices in dialysis settings may depend essentially on overcoming barriers identified by the pharmacists, such as time

constraints, support from hospital administration and, most importantly, willingness from both patients and health professionals to actively participate in dialogues to resolve medication-related issues in patients undergoing dialysis. Delivering adherence support activities by the pharmacists will also depend upon the knowledge and skills acquired through tailored education, training and routine practices [260, 261]. Pharmacists in this survey unanimously disagreed that they lack knowledge or skills for assessing and promoting adherence; instead they were highly confident about conducting such activities. Pharmacists possess advanced skills in clinical pharmacotherapy and delivering pharmaceutical care services, such as optimising medication regimens, assessing adherence and educating patients and allied healthcare teams on medication-related issues. These skills are integral to their role [262] and could have contributed to a higher confidence scoring.

Not surprisingly, the majority of the pharmacists were of the opinion that dedicated renal pharmacists should be assigned to undertake adherence assessment activities in dialysis settings. This could be viewed as a biased attitude towards their professional role, although past reports have shown that other allied health professionals who worked in collaboration with the pharmacists in the past were more aware of the competency and contribution of pharmacists in delivering pharmaceutical care services and were more likely to recommend them being assigned to clinical wards [263-265]. Pharmacists' intervention has contributed to reduced hospitalisation, improved patient satisfaction and decreased overall treatment costs in patients undergoing dialysis [245]. Moreover, the presence of a pharmacist in dialysis settings can be complementary to helping patients with their medication management, educating and counselling about medicines and life style changes through motivational

interviews, providing advice for their minor ailments and most importantly, identifying medication issues and promoting adherence [245].

Current Australian outpatient dialysis settings have limited access to fully-fledged renal pharmacy services [245]. Outpatient dialysis centres provide pharmacy services on an as required basis where pharmacists may be requested for medication reviews but only in situations when the patients' conditions demand higher scrutiny of their medication regimen. Although inclusion of dedicated professionals who could solely focus on medication management and adherence promotion would be an ideal solution, it is unlikely that this provision would be incorporated into dialysis settings in the near future. Various factors may hinder the sustainability of such programs including the limitations of time and resources [111], funding and organisational priorities [245, 266]. Our findings hint towards the pharmacists' longing for becoming active team members to provide medication management services to the patients in outpatient dialysis settings. Another possibility would be to empower the predominant nursing faculty available in the dialysis settings, as they are the professionals closely interacting with the patients on a daily basis and are ideally placed for delivering medicines, monitoring patient progress, and engaging patients in strategies to promote adherence [139, 267]. Nevertheless, we may need to consider carefully the existing workload of the renal nurses and barriers to successful incorporation of auxiliary roles, such as adherence assessment and promotion activities for the patients undergoing dialysis.

5.8.1. Study Limitations

The study sample in this survey was low. However, the sample is considered representative as it was purposefully targeted at the members of the professional forum that largely constitutes specialist renal pharmacists in Australia. As individual practices may vary between the dialysis centres and many of the outpatient dialysis centres do not have pharmacist representation, the survey findings may not be generalisable. Furthermore, no *a priori* hypothesis was set during the conduct of this study. Items were also not generated by qualitative interviews and factor analysis, nor was there principal component analysis for item reduction attempted. Hence, this study has numerous measure variables. Nevertheless, being a first study of its kind and having a detailed questionnaire to measure renal pharmacists' perceptions on the issue of medication nonadherence, this exploratory study may provide a baseline observation for informing future studies.

5.9. Conclusion

Pharmacists were rarely assigned to assessing adherence in dialysis settings. Established self-reporting methods to measure adherence were under-utilised, compared with objective blood monitoring. Pharmacists were supportive of dedicating more time to assess and promote adherence, although important barriers such as lack of both time and administrative support, were preventing the conduct of these activities. Having renal-specialised pharmacists in dialysis centres could facilitate adherence promotion and early identification of medication-related issues in patients undergoing dialysis.

Supplementary Data

Appendix 10. The STROBE checklist

Appendix 11. Survey Questionnaire

Appendix 12. Inter-item correlation matrix and Cronbach's alpha coefficients for each scales

Appendix 13. Comments on perceptions and current practices

CHAPTER SIX

6. RENAL NURSES' PERCEPTIONS AND CURRENT PRACTICES OF ASSESSING MEDICATION ADHERENCE IN DIALYSIS PATIENTS: A CROSS-SECTIONAL SURVEY

6.1. Abstract

Background: Renal nurses play a vital role in caring for ESKD patients undergoing dialysis. Despite the high prevalence of medication nonadherence in patients undergoing haemodialysis, little is known about renal nurses' perceptions and the current practices of assessing adherence in routine patient care.

Objectives: To develop a survey tool and measure renal nurses' perceptions, current practices, and barriers to assessing medication adherence in patients undergoing haemodialysis.

Design: A cross-sectional survey design.

Settings: Australian dialysis centres.

Participants: Study participants were renal nurses working in Australian dialysis centres.

Methods: Participants completed an online survey during March, April, and May 2016. The survey included five psychometric scales that measured the perceived prevalence of and contributors to nonadherence, the effectiveness of various methods, the barriers to adherence, and the participants' confidence to assess adherence using a 10-point Likert scale (1 = strongly disagree, 10 = strongly agree). Current adherence

measuring practices were captured using a 4-point graded response (1 = do not practice at all to 4 = practice for every patient).

Results: A total of 113 renal nurses completed the survey. The majority of nurses agreed that patients in their unit are not adherent to their medicines (74.5%, n = 82; median = 8.0). Most nurses agreed that having dedicated professionals conducting medication history interviews can be effective in identifying nonadherence (88.9%, n = 96; median = 8.0). Objective blood monitoring was the most frequently used method to determine nonadherence (83.2%, n = 89), with little attention being paid to patients' self-reports of adherence (55.1%, n = 59). Lack of time, support from hospital administration, and patients' disinterest in discussing medication-related issues with the nurses were perceived as barriers to assessing adherence.

Conclusions: Established self-report methods for measuring medication nonadherence were under-utilised by the renal nurses, whereas objective blood monitoring was routinely used. Overcoming renal nurses' work-related barriers may facilitate the effective monitoring and promotion of medication adherence in patients undergoing chronic dialysis.

Keywords: Adherence assessment practices; cross-sectional survey; dialysis; Kidney failure, chronic; medication adherence; renal nurses

6.2. Contribution of the Paper

What is already known about the topic?

- Medication nonadherence in chronically ill patients is a major determinant of poor patient outcomes.
- Adherence research has been primarily focused on understanding and changing the medication-taking behaviour of patients, with little attention being paid to understanding the healthcare system's inadequacies in addressing such behaviour.
- Little is known about the renal nurses' practices of assessing medication adherence during the routine care of patients undergoing dialysis.

What this paper adds?

- Renal nurses rely on routine laboratory results to detect medication nonadherence, with little to no attention being paid to patient engagement via self-reported measures.
- Lack of time, support from hospital administration, and patients' disinterest in communicating medication-related issues to renal nurses were perceived as barriers to assessing adherence.
- Renal nurses believed that having dedicated renal pharmacists in dialysis centres would facilitate assessment and the promotion of medication adherence in patients undergoing dialysis.

6.3. Introduction

Medication nonadherence often leads to poor patient outcomes in chronic diseases [202]. The negative impact of nonadherence is such that alleviating it would result in greater public health gains than developing newer, costly therapies [202, 268]. The reasons for nonadherence depend on the disease and the complexity of the regimens prescribed [2]. CKD patients in general, and patients receiving dialysis in particular, are at high risk of medication nonadherence. This may be due to an increased burden of concomitant illness and dialysis-associated complications, leading to an increased complexity of various treatment regimens [229].

Overall, half of dialysis-treated patients are nonadherent to at least part of their treatment regimen, with medication nonadherence ranging between 12.5% and 98.6% [23, 139]. The deterioration of the underlying disease conditions in patients undergoing dialysis following medication nonadherence has been associated with increased mortality and recurrent hospitalisations, placing a substantial economic burden on the healthcare system [23].

The current research on medication adherence primarily focuses on understanding and changing the medication-taking behaviour of patients, rather than on understanding and changing the healthcare system inadequacies that may affect adherence in patients [110, 111]. Patients who had shorter consultations with their doctor or a healthcare professional that lacked a discussion on medication-related issues were found to be nonadherent to their prescribed treatment [225, 232]. Engaging patients in a meaningful conversation about their medication use may not be a straightforward solution to this problem. Healthcare professionals have reported time availability and work pressures as barriers to assessing a patient's ability to take medications, and to investigating any impediments to medication adherence [232].

Despite extensive research on the incidence, measurement, and improvement of medication adherence [2], little is known about the actual practices of measuring adherence in clinical settings. The extent to which renal nurses are aware of adherence measurement practices, and how much time is devoted to measuring and promoting adherence in patients undergoing dialysis, is unknown. Renal nurses working with patients get to know them well as they see them frequently, usually three times a week for a period of three-to-five hours a day. Such an engagement provides an excellent opportunity for the renal nurses to educate and encourage medication adherence in patients undergoing dialysis.

Nevertheless, an understanding of renal nurses' perceptions of medication nonadherence in patients undergoing dialysis, and the likely barriers to monitoring and improving medication adherence is essential before nurses can take part in any quality initiative targeting nonadherence. Therefore, we aimed to understand the renal nurses' perceptions, current practices, and barriers to assessing medication adherence in patients undergoing dialysis.

6.4. Methods

6.4.1. Study Design

An online cross-sectional survey method was used. We followed the STROBE guidelines for the design and reporting of this study [14]. The STROBE checklist is supplied in **Appendix 14.**

6.4.2. Setting and Recruitment of Participants

All renal nurses currently registered to practice in Australian dialysis settings were eligible to participate. Recruitment was sought through the professional renal association, the Renal Society of Australasia (RSA). Recruiting participants directly was not feasible due to a lack of assured means of identifying renal nurses involved in the care of patients undergoing dialysis, therefore we sought participant recruitment through a professional organisation.

6.4.3. Data Collection

An online survey was conducted for a period of three months between March and May 2016. We coordinated with the professional association to send an invitation flyer that described the study's aims, and which gave a web address for the survey, to dialysis nurses through email alerts, social media posts, and e-newsletters. Reminders were sent on a fortnightly basis. After the survey was completed, we randomly selected eight participants who had opted in to win gift vouchers valued at AUD $100 for their contribution.

6.4.4. Development of Survey Instrument

We utilised a previously developed survey instrument (Chapter 5) that measured renal pharmacists' perceptions and practices of assessing medication adherence in dialysis patients [269]. To briefly describe the instrument, it comprised seven sections that explored demographics, perceptions of the prevalence of, and contributors to nonadherence, the perceived effectiveness of methods used to detect nonadherence, barriers to adherence assessment, and participants' confidence in assessing

adherence. A 10-point Likert scale of agreement was used to measure perception (1 = strongly disagree, 10 = strongly agree). The last section comprised questions related to the current practices of assessing adherence in dialysis patients, and used four-point graded response where one meant “do not practice”, and four meant “practice for every patient”. The survey questionnaire is supplied in **Appendix 11**.

6.4.5. Statistical Analysis

Data were entered and analysed in SPSS version 23.0 (IBM Corp., Armonk, N.Y., USA). Demographic characteristics were ascertained through descriptive analysis. Kolmogorov-Smirnov and Shapiro-Wilks tests were performed to assess normality. Continuous variables were summarised using the median and the inter quartile range (IQR). Mann-Whitney or Kruskal-Wallis tests was performed to detect the differences in median scores for non-normally distributed data. The Dunn-Bonferroni test was used to identify statistically significant differences between intergroup variables, as a post-hoc analysis [256]. Cronbach’s alpha coefficient was used to measure the internal consistency reliability of the perception scales. A p value of < 0.05 was considered statistically significant.

6.4.6. Ethical Considerations

Ethics approval was granted by the Tasmanian Social Sciences Human Research Ethics Committee (reference number: H0015433). Completing the survey itself was considered implied consent to participate in this study.

6.5. Results

A total of 113 renal nurses completed the survey. The majority of the participants were female (92.0%, n = 104), with 11-20 years of experience in renal units (47.8%, n = 54). As participants were recruited indirectly through the RSA, which has over 1800 members, including nurses, technicians, social workers, dietitians, and other allied health professionals; we could not gauge the actual survey response rate for renal nurses alone. Nevertheless, this study was not aimed at generalisability, but for developing and piloting the survey instrument to inform larger nation-wide studies in dialysis settings. The characteristics of the respondents are presented in **Table 15**.

Table 15. Demographics of survey respondents (n = 113)

Variable	**Category**	**N (%)**
Age, Years		47 (range, 25-66)
	20-30	6 (5.3)
	31-40	24 (21.2)
	41-50	39 (34.5)
	≥ 51	44 (38.9)
Gender		
	Male	9 (8.0)
	Female	104 (92.0)
Level of education		
	Diploma	11 (9.7)
	Bachelors	48 (42.5)
	Graduate certificate	46 (40.7)
	Masters and doctorate	8 (7.1)
Designation		
	Enrolled Nurse	2 (1.8)
	Registered Nurse	76 (67.3)
	Nurse Practitioner	7 (6.2)
	Nurse Unit Manager	28 (24.8)
Experience in renal unit, Years		14 (range, 1-36)
	1-10	43 (38.1)

Variable	Category	N (%)
	11-20	54 (47.8)
	≥ 21	16 (14.2)
Australian State		
	Victoria	55 (48.7)
	Queensland	16 (14.2)
	Tasmania	16 (14.2)
	New South Wales	13 (11.5)
	Other States	13 (11.5)
Organisation type		
	Public	99 (87.6)
	Private	14 (12.4)
Dialysis unit location		
	Metropolitan	52 (46.0)
	Rural	61 (54.0)
Characteristics of dialysis unit		
	Number of dialysis chairs (n = 111)	12 (range, 3-32)
	Number of 1.0 FTE nurse (n = 79)	4 (range, 1-16)
	Presence of nursing educator, Yes	49 (43.4), 0.6 FTE (range, 0.3-1.0)
	Presence of pharmacist, Yes	25 (22.1), 1.0 FTE (range, 0.4-1.0)
	In-centre haemodialysis service (HD)	83 (73.5)
	Peritoneal dialysis service (PD)	2 (1.8)
	Home haemodialysis (Home HD)	1 (0.9)
	All services (HD, Home HD, PD)	27 (23.9)

Note: For continuous variables, median (range); for categorical variables, numbers with percentage in parentheses; *Abbreviation:* FTE, full-time equivalent of service

6.5.1. Internal Consistency Reliability of Scales

The overall reliability comprising all five scales demonstrated a good level of internal consistency, with an alpha of 0.84. The reliability coefficients for each scale were as follows: perceived prevalence scale (0.85), perceived contributors (0.83), perceived effectiveness (0.67), perceived barriers (0.70), and participant' confidence (0.90).

Appendix 15 contains the particulars of the Inter-Item Correlation Matrix, and Cronbach's alpha coefficients for each scale.

6.5.2. Perceived Prevalence and Contributors of Nonadherence

The majority of renal nurses believe that patients in their unit often forget to take their medicines (median = 8.0), rarely ask questions about medicines (median = 7.0), are unable to answer medicine-related questions (median = 7.0), and are often confused about their medicines (median = 7.0). The majority of the nurses thought that limited understanding of their disease (median = 7.0), being prescribed with complex medication regimens (median = 7.0), lacking family or social support (median = 7.0), having low educational backgrounds (median = 7.0), and low income (median = 7.0) contributed to medication nonadherence in patients undergoing dialysis. The majority of the participants disagreed that being older (median = 4.0) or male (median = 5.0) contributed to nonadherence behavior, however (**Table 16**).

Table 16. Perceived prevalence and contributors of nonadherence in patients undergoing dialysis

Statements	Participant's Response, n (%)		Median (IQR)
Perceived prevalence	**Scoring ≤ 5**	**Scoring ≥ 6**	
Have limited understanding of their medications (n = 112)	48 (42.9)	64 (57.1)	6.0 (4.0-7.75)
Rarely ask questions about medications (n = 112)	39 (34.8)	73 (65.2)	7.0 (4.0-8.0)
Do not take their medications as prescribed (n = 112)	50 (44.6)	62 (55.4)	6.0 (4.0-7.0)
Stop taking some medications when feel better (n = 111)	53 (47.7)	58 (52.3)	6.0 (3.0-7.0)
Are often confused about medicines (n = 111)	42 (37.8)	69 (62.2)	7.0 (5.0-8.0)
Change dose/dosing interval that suits lifestyles (n = 111)	54 (48.6)	57 (51.4)	6.0 (3.0-7.0)
Express difficulty in swallowing larger pills (n = 111)	51 (45.9)	60 (54.1)	6.0 (3.0-8.0)
Don't believe current medicines are helping (n = 111)	74 (66.7)	37 (33.3)	4.0 (3.0-6.0)
Can't answer questions about medications (n = 111)	40 (36.0)	71 (64.5)	7.0 (4.0-8.0)
Forget to take medications sometimes (n = 110)	28 (25.5)	82 (74.5)	8.0 (5.0-9.0)
Perceived contributors			
Older patients are more nonadherent (n = 110)	91 (82.7)	19 (17.3)	4.0 (2.0-5.0)
Male patients are more nonadherent (n = 110)	74 (67.3)	36 (32.7)	5.0 (3.0-7.0)
Patients with multiple co-morbidities (n = 109)	47 (43.1)	62 (56.9)	6.0 (5.0-8.0)
Patients lacking family/social support (n = 109)	31 (28.4)	78 (71.6)	7.0 (5.0-8.0)
Patients having low income (n = 109)	39 (35.8)	70 (64.2)	7.0 (5.0-8.0)
Patients having low level education background (n = 109)	32 (29.4)	77 (70.6)	7.0 (5.0-8.0)
Having different language/cultural background (n = 108)	37 (34.3)	71 (65.7)	7.0 (5.0-8.0)
Having limited understanding of disease state (n = 109)	24 (22.0)	85 (78.0)	7.0 (6.0-8.0)
Patients not satisfied with their treatment/care (n = 109)	44 (40.4)	65 (59.6)	6.0 (4.0-8.0)
Patients with complex medication regimens (n = 109)	31 (28.4)	78 (71.6)	7.0 (5.0-9.0)

Note: Perception measured on a scale of 1-10, Where 1 = strongly disagree and 10 = strongly agree;
Abbreviation: IQR, Inter-quartile range.

6.5.3. Perceived Effectiveness and Barriers to Assessing Adherence

The majority of renal nurses agreed that having dedicated professionals who take medication histories (median = 8.0), or having pharmacists who conduct medication reviews and reconciliations (median = 9.0) can be effective in assessing adherence. High median ratings were also observed for the effectiveness of assessing adherence through objective methods, such as blood monitoring or physical assessment (median = 8.0), and through subjective methods, such as conducting medication history interviews (median = 8.0).

Renal nurses disagreed that they lacked the knowledge and skills to assess adherence (median = 2.0), but over one-third perceived that they lacked the time needed to undertake adherence promoting activities (median = 4.0). Furthermore, over a third of the participants reported that there is no support from hospital administration in conducting adherence promoting activities (median = 5.0). Nearly a quarter of the nurses also perceived that patients are not interested in discussing medication-related issues with them (median = 3.0) (**Table 17**).

6.5.4. Participants' Confidence in Assessing Adherence

Renal nurses' median confidence ratings were higher in terms of ability to suggest strategies to improve adherence (median = 8.0), followed by ability to assess patients' knowledge and beliefs about medicines (median = 8.0), conduct a medication history interview (median = 8.0), and provide medication counselling (median = 8.0) (**Table 17**).

Table 17. Perceived effectiveness, barriers and confidence to assess adherence in patients undergoing dialysis

Statements	Participant's Response, n (%)		Median (IQR)
Perceived effectiveness	**Scoring ≤ 5**	**Scoring ≥ 6**	
Interviewing patients to obtain medication history (n = 108)	19 (17.6)	89 (82.4)	8.0 (6.0-9.0)
Asking patient's family/carer about medication (n = 108)	14 (13.0)	94 (87.0)	7.0 (6.0-8.0)
Measuring objective indicators such as SPL/BP (n = 108)	14 (13.0)	94 (87.0)	8.0 (7.0-9.0)
Asking patients to bring medications and count (n = 107)	45 (42.1)	62 (57.9)	7.0 (4.0-8.0)
Having a dedicated professional to take medication history (n = 108)	12 (11.1)	96 (88.9)	8.0 (7.0-9.0)
Conducting medication reviews and reconciliation by Pharmacist (n = 108)	14 (13.0)	94 (87.0)	9.0 (8.0-10.0)
Perceived barriers			
Lack of knowledge and skills to assess nonadherence (n = 108)	96 (88.9)	12 (11.1)	2.0 (2.0-3.0)
Lack of time (n = 108)	67 (62.0)	41 (38.0)	4.0 (2.0-7.0)
Not my role (n = 106)	102 (94.4)	6 (5.6)	2.0 (1.0-3.0)
Patient's disinterest on discussing medication issues (n = 108)	82 (75.9)	26 (24.1)	3.0 (2.0-5.0)
No support from hospital administration (n = 106)	66 (62.3)	40 (37.7)	5.0 (2.0-8.0)
Never thought about adherence before this survey (n = 108)	101 (93.5)	7 (6.5)	1.0 (1.0-2.0)
Participants' confidence			
Ability to conduct a medication history interview *(n = 108)*	16 (14.8)	92 (85.2)	8.0 (7.0-9.0)
Ability to provide medication counselling *(n = 108)*	21 (19.4)	87 (80.6)	8.0 (6.0-9.0)
Ability to clarify patient's medication queries *(n = 108)*	17 (15.7)	91 (84.3)	7.0 (6.0-9.0)
Ability to suggest strategies to improve adherence *(n = 108)*	8 (7.4)	100 (92.6)	8.0 (7.0-9.0)
Ability to assess patient's knowledge and beliefs about medications *(n = 108)*	14 (13.0)	94 (87.0)	8.0 (7.0-9.0)

Note: Perception measured on a scale of 1-10, Where 1 = strongly disagree and 10 = strongly agree;
Abbreviation*:* IQR, Inter quartile range; SPL, serum phosphate levels; BP, blood pressure.

6.5.5. Differences in Perceptions Based on Study Demographics

Participant age significantly affected their median scores on perceived barriers ($\chi 2$ (3, N = 108) = 11.52, p < 0.01). Younger nurses, aged 20-30 years perceived more barriers than their elder counterparts aged 41-50 years (median: 4.5 vs 2.0, p < 0.05), and ≥ 51 years (median: 4.5 vs 2.25, p < 0.05). Similarly, significant differences were observed in perceived contributor scores based on professional designation ($\chi 2$ (2, N = 108) = 6.76, p < 0.05). Registered nurses perceived more contributors to nonadherence than the nurse unit managers (median: 7.0 vs 5.0, p < 0.05). Participants' experiences in renal units also influenced their confidence scores ($\chi 2$ (2, N = 108) = 6.21, p < 0.05). Nurses with 1-10 years of experience were less confident in assessing adherence than participants with 11-20 years (median: 7.0 vs 8.0, p < 0.05), and with ≥ 21 years (median: 7.0 vs 8.0, p < 0.05) of experience (**Table 18**).

Table 18. Differences in perceptions based on study demographics across all scales

Variables	Perceived prevalence		Perceived contributors		Perceived effectiveness		Perceived barriers		Participants' confidence	
	Median	Mean Rank	Median	Mean Rank	Median	Mean Rank	Median	Mean Rank	Median	Mean Rank
Age, years [a]										
20-30	6.5	76.3	7.0	55.2	8.5	73.3	4.5	93.1**	7.0	33.9
31-40	6.25	53.7	7.0	60.7	8.0	56.2	3.0	62.9	8.0	54.2
41-50	6.0	54.8	6.5	54.3	8.0	58.0	2.0	49.2	8.0	56.2
≥ 51	6.25	56.8	7.0	53.7	7.75	48.3	2.25	49.8	8.0	55.6
Gender [b]										
Male	6.0	52.7	6.5	59.8	8.25	58.6	2.0	48.6	7.5	57.0
Female	6.0	56.8	7.0	55.2	8.0	54.2	3.0	55.0	8.0	54.3
Level of education [a]										
Diploma	5.75	49.7	5.5	42.4	7.0	38.6	3.0	51.8	7.0	38.5
Bachelors	6.0	51.2	6.75	55.3	8.0	61.3	2.5	54.2	8.0	55.7
Graduate certificate	6.5	60.0	7.0	57.7	8.0	49.4	3.0	57.0	8.0	55.2
Masters and doctorate	7.75	78.1	7.0	63.1	8.25	63.1	2.0	46.1	8.0	63.6
Designation [a]										
Registered nurse	6.25	56.7	7.0	59.9*	8.0	54.8	2.75	54.1	8.0	51.7
Nurse practitioner	5.5	44.3	5.5	42.1	7.0	32.3	3.5	69.7	7.0	45.7
Nurse unit manager	6.5	55.2	5.0	43.5	8.0	55.5	2.0	47.8	8.0	60.3
Experience in renal unit, Years [a]										
1-10	6.0	54.8	7.0	56.8	8.0	55.6	3.0	60.8	7.0	45.2*
11-20	6.5	60.5	7.0	80.6	8.0	55.4	2.0	48.6	8.0	59.7
≥ 21	6.0	47.1	6.0	56.0	7.75	48.2	3.0	58.4	8.0	62.3

Note: Perception measured on a scale of 1-10, where 1 = strongly disagree and 10 = strongly agree

[a] Kruskal-Wallis Test. [b] Mann-Whitney Test.

* $P < 0.05$; ** $P < 0.01$

6.5.6. Current Practices of Assessing Adherence

Figure 13 depicts the renal nurses' reports on current adherence assessment practices in dialysis centres. Assessing adherence objectively through blood results or physical assessment was routinely conducted for every patient (83.2%, n = 89). The majority of the participants reported that pharmacists were not available for medication reviews and reconciliation activities (65.1%, n = 69), and nearly half of the participants mentioned that dedicated professionals were not assigned to conducting medication history interviews (46.7%, n = 49). Similarly, only around half of the participants (55.1%, n = 59) reported that medication history interviews were conducted for every patient. Patients' families or carers were asked about medications for only some patients with a higher risk of adverse effects (45.8%, n = 49). Similarly, asking patients to bring medications and counting them was mainly practiced in high-risk patients (33.0%, n = 35).

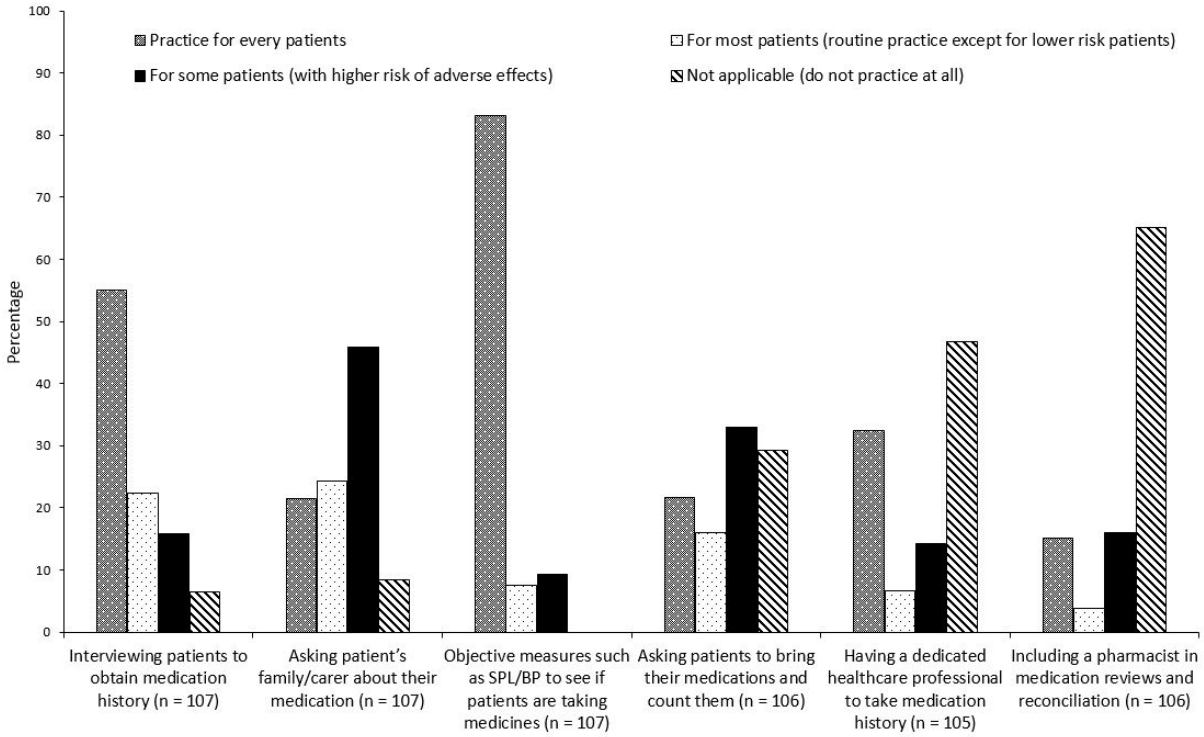

Figure 13. Nurses' reports on current practices of assessing medication adherence in patients undergoing dialysis in Australia

6.5.7. Qualitative Comments

The qualitative comments reinforced the survey findings regarding contributors of nonadherence, such as lack of knowledge about medicines, comorbid illnesses, tablet burden, culture and communication barriers, forgetfulness, lack of support, and relative affordability of medicines. Renal nurses also highlighted the need for a sustainable strategy to empower self-management in patients taking long-term medications. There was a recurring theme in the desire for a designated renal pharmacist in dialysis settings to manage medication-related issues. Furthermore, participants reported that patients trusted their doctors with medical decisions, and preferred communicating with them rather than with nurses. Due to long waiting times

for consultations, however, their medication-related queries remain unanswered. This subsequently nurtured nonadherence behaviour in patients undergoing dialysis. The comments are given in **Appendix 16**.

6.6. Discussion

We reported renal nurses' perceptions on assessing medication adherence in patients undergoing dialysis. The internal consistency and reliability of the overall scale was good. The findings from this study suggest that current adherence assessment practices are suboptimal, and the methods used to screen patients' medication-taking behaviour are used less in dialysis settings. Renal nurses seemed to be confident in conducting adherence assessment activities, and their level of confidence increased with increased work experience. Lack of time, lack of support from hospitals, and patients' disinterest in discussing medication-related issues with the renal nurses were perceived as barriers to assessing adherence. The majority of the nurses acknowledged that having a dedicated pharmacist would be effective in promoting adherence activities, but these services are rarely available in dialysis centres.

Health professionals are often overly optimistic about adherence behaviour in their patients [250], however, renal nurses in this study acknowledged the high prevalence of nonadherence behaviour in patients undergoing dialysis. Nurses' perceptions corroborated with earlier findings that patient-related factors, such as lack of knowledge about medicines, lack of family or social support, forgetfulness, comorbid conditions, pill burden, relative affordability, and culture and communication barriers could influence adherence [141, 226, 228, 252].

Renal nurses also emphasised that sustainable strategies for empowering self-management in patients taking long-term medications, and having trusted relationships with healthcare providers, can have a significant influence on patients' medication-taking behaviour. Patients become truthful about taking medication only if they feel free to admit their difficulties with no risk of criticism, and when there is a true partnership with their healthcare providers [259].

Patients with CKD who express dissatisfaction due to an absence of guidance and a lack of discussion about medication-related issues during consultations are found to be less motivated to follow treatment recommendations, to hide their concerns, and to acquire nonadherence behaviours [225]. Therefore, it is imperative that renal healthcare professionals routinely instigate discussions on medication-related issues with the patients undergoing dialysis.

A recent systematic review of trials that assessed the effects of nursing interventions on improving medication adherence among discharged, home-dwelling and older adults suggested that nurse-led and nurse-collaborative interventions moderately improved medication adherence in discharged older adults [270]. Similarly, a nurse-delivered, self-care intervention program for chronic heart failure patients has been found to be effective in improving patients' medication adherence [271]. Designing nurse-led tailored interventions suitable for use during dialysis sessions that educate patients on problem-solving, guide behavioural change, and teach them to take action in response to wavering signs and symptoms, can be an effective self-management strategy for improving medication adherence in patients undergoing dialysis [226].

We observed that current adherence assessment practices are limited, and that the methods used to monitor nonadherence behaviour, such as medication history taking, and medication reviews and reconciliation by pharmacists, were only occasionally conducted, whereas objective blood monitoring was a routine practice in most settings. A recent survey on renal pharmacists' perceptions corroborated the study's findings on current adherence assessment practices in dialysis settings [269].

Objective blood monitoring in patients undergoing dialysis is mainly conducted to ensure that the dialysis prescription, i.e. the time and type of the dialysis treatments, are optimal. Although we can also draw inferences from blood results to see if patients are adherent to their medications, particularly phosphate binders, the reliability of these results can be questioned as they can be affected by various dietary and clinical factors. A preferable approach would be to combine objective measures with subjective ones, such as patient interviews or validated adherence assessment questionnaires [252]. This may also help to overcome the subjective bias of patient self-reports [208, 272].

The ability to conduct adherence assessments and promotion activities in dialysis settings may largely depend upon overcoming the barriers identified in this study, such as time and resource limitations, a lack of hospital support, and most importantly unwillingness from both patients and health professionals to actively participate in dialogues to resolve medication-related issues. The delivery of adherence support activities by renal healthcare professionals will also depend upon the knowledge and skills they acquire through tailored education and training, and routine practices [260, 261]. Renal nurses in this study largely disagreed that they lack the knowledge and skills needed to conduct adherence assessment activities, and were instead highly confident about this.

The fact that renal nurses are involved in managing and assessing the health needs of the dialysis patients on a daily basis, and in educating patients about their diseases, prognoses, and treatments may have contributed to higher confidence scoring. Not surprisingly, the majority of the renal nurses also endorsed the inclusion of dedicated professionals, especially renal pharmacists, in undertaking adherence assessment activities in patients undergoing dialysis. Positive perceptions towards pharmacists' roles may be due to past experiences of inter-professional collaborations, and awareness of the competency and contribution of pharmacists in delivering pharmaceutical care services [263-265]. Pharmacist interventions have contributed to reduced hospitalisation, improved patient satisfaction, and decreased overall treatment costs in patients undergoing dialysis [245].

The availability of renal pharmacy services in Australian outpatient dialysis centres is extremely limited [245]. Centres receiving pharmacy services on a necessary basis might call upon pharmacists for medication reviews only on occasions when the severity of a patient's condition demands higher scrutiny of their medication regimen. Although the presence of a dedicated professional or renal specialised pharmacist who can solely focus on medication management and adherence promoting activities would be an ideal solution, it is unlikely that this will be incorporated into every dialysis centre anytime soon due to time and resource availability [111], finances, and organisational factors [245, 266].

Alternative measures include empowering the existing renal nursing services available in the dialysis centres as they are the professionals who closely interact with the patients, and are ideally placed to deliver medicines, monitor patient progress, and engage patients in strategies to promote adherence [139, 267]. Unfortunately, the existing workload of the renal nurses and the barriers to successful incorporation of

auxiliary roles, such as adherence assessment and promotion activities, need to be carefully considered in dialysis settings. Moreover, dedicated pharmacists should make an effort to educate patients on self-management activities that promote adherence and contribute to positive health outcomes in patients undergoing dialysis [273].

6.6.1. Study Limitations

Participants were not directly recruited, instead email alerts, e-newsletters, and social media posts from the professional organisation were relied upon. As such, an absolute denominator for the survey response rate could not be ascertained. This may have led to the inclusion of self-selected participants who were more interested in sharing their perceptions. Nevertheless, an even amount of participation was observed from rural and metropolitan areas, as well as from public and private dialysis centres.

The study findings may not be generalisable to dialysis settings across Australia, for example, New South Wales has the highest number of dialysis centres, but there was poor representation from the renal nurses. Nevertheless, the scope of this study was mainly to generate baseline observations to inform larger nation-wide surveys.

6.7. Conclusion

Clinicians spend a great deal of time prescribing the best possible medications for their patients, yet little attention is paid to measuring adherence and ensuring that patients are adhering to their prescribed medications. The current adherence assessment practices of renal nurses are limited to selective patients utilising objective laboratory-based values instead of patient self-reported measures. Lack of time, administrative

support, and patient disinterest in communicating medication issues with the renal nurses, were commonly perceived as barriers to assessing adherence. Strengthening renal nursing services by addressing the existing barriers may be a way to improve medication adherence in patients undergoing haemodialysis.

Supplementary Data

Appendix 14. The STROBE checklist

Appendix 15. Inter-item correlation matrix and Cronbach's alpha coefficients for each scales

Appendix 16. Comments on perceptions and current practices

CHAPTER SEVEN

7. BARRIERS TO ASSESSING ADHERENCE AND CONSIDERATIONS TO IMPROVE ADHERENCE ASSESSMENT PRACTICES IN DIALYSIS SETTINGS: A QUALITATIVE STUDY

7.1. Abstract

Background: End-stage kidney disease (ESKD) patients undergoing dialysis are typically prescribed multiple complex medication regimens; as such, they are at high risk of medication nonadherence. Current clinical practices focuses on prescribing the best possible medications for their patients. However, little attention has been given towards measuring and ensuring patients' adherence to the prescribed treatment. The aims of this study were to explore barriers to assessing adherence in patients undergoing dialysis, and identify strategies to improve adherence assessment practices in dialysis settings.

Study Design: Qualitative study.

Setting & Participants: 18 health professionals (12 renal nurses and 6 specialist renal pharmacists) working in Australian dialysis settings.

Methodology: Semi-structured individual interviews conducted between November and December 2016.

Analytical Approach: Transcripts were thematically analysed using Braun and Clarke's six-step method of conducting thematic analyses.

Results: Participants were 25-60 years old, and had 1-27 years of experience working in dialysis settings. Seven themes related to barriers to assessing medication adherence were identified: prioritisation of resources, interplay between workload and available time, awareness of formalised adherence measures and training deficits, concerns around practicality/suitability of adherence measures, communication of assessment services, patient participation, and trust. Three themes related to strategies to improving adherence assessment practices were identified: formalisation of the adherence assessment process, integration of assessment processes/tools into routine, and use of multidisciplinary support to assess medication-taking behaviour in patients undergoing dialysis.

Limitations: Individual practices may vary between dialysis settings; as such, the views expressed by the participants may not be generalisable to other settings.

Conclusions: Current adherence assessment practices could be improved through formalisation and integration of the assessment process into hospital policy/procedures. Additionally, as barriers to assessing adherence were identified at organisational, professional and patient levels, there is a need to address barriers from each level in order to improve adherence assessment practices in dialysis settings.

INDEX WORDS: Adherence assessment practices; barriers; dialysis; kidney failure, chronic; medication adherence; qualitative research; health care professionals.

7.2. Introduction

Medication nonadherence is a well-recognised problem in chronic diseases with the global prevalence rate estimated at 50% [16]. Avoidable health care costs attributed to medication nonadherence in the US is estimated between $100 and $300 billion annually that represents between 3% and 10% of the total US health care costs [274]. End-stage kidney disease (ESKD) patients undergoing chronic haemodialysis are at high risk of medication nonadherence, due to increased burden of concomitant illness and dialysis-associated complications that demands complex treatment regimens [8, 23]. The prevalence of medication nonadherence in patients undergoing haemodialysis range between 12.5% and 98.6% [23]. Poor adherence has led to increased morbidity and mortality [8, 142, 143], repeat admissions [142], and unwanted treatments [143] in patients undergoing dialysis.

The primary step towards improving medication adherence involves true assessment of whether patients have followed their prescribed regimens [275]. Providing an opportunity for patients to express their concerns with their health professionals can help elicit information regarding patients' beliefs and attitudes towards medications, social and cultural contexts, and emotional health challenges that may impede adherence [2, 275, 276]. All of these components are crucial in influencing adherence intentions, and thus need to be explored and discussed during therapeutic consultations [275]. However, current clinical practices focus more on improving treatment outcomes rather than ensuring patient’s adherence to prescribed regimens [1], despite the known associations between poor adherence and morbidity and mortality rates. As proper assessment of patients' adherence is important to ensure the benefits of prescribed therapies, an ongoing assessment of adherence is necessary to ensure that patients are taking their medications appropriately [1, 275].

Patients with ESKD often undergo haemodialysis three times a week for at least 3-5 hours per day [277]. This provides a unique opportunity for renal health care professionals to interact with their patients. Renal professionals can seize this opportunity to assess adherence, educate patient, and promote medication adherence in patients undergoing dialysis. However, no prior studies have explored renal professionals' perceptions regarding adherence assessment practices in dialysis settings. Understanding renal professionals' perspectives can help identify underlying challenges and potential practical ways by which adherence measurement practices could be improved.

Therefore, the present study aims to explore the perspectives of renal professionals in regard to medication adherence assessment practices. Specifically, the present study aims to qualitatively:

1. Explore barriers to assessing adherence, and
2. Identify strategies to improve adherence measurement practices in Australian dialysis settings.

7.3. Methods

This qualitative study followed the consolidated criteria for reporting qualitative research (COREQ) guideline [15] during its conduct and reporting (**Appendix 17**). The Tasmanian Social Sciences Human Research Ethics Committee granted the ethics approval (reference no. H0015433).

7.3.1. Participants

Renal professionals including pharmacists and nurses working in Australian dialysis centres were eligible to participate. Recruitment was sought from participants who had previously participated in a cross-sectional survey of renal professionals that measured perceptions and current practices of assessing medication adherence in patients undergoing dialysis. Twenty renal professionals from the survey study expressed their interest to participate in the present study, however, two participants later retracted due to lack of time.

7.3.2. Data Collection and Analysis

A pharmacist researcher (SG) conducted semi-structured individual phone interviews with the participants between November and December 2016 (Interview guide: **Appendix 18**). One-on-one interview was mainly chosen as the research required to generate insights based on personal perspectives that are unlikely to be shared in a group discussion. Also, due to the busy schedule of the participants it was practically not feasible to make focus groups a realistic option. SG has been trained in qualitative research, and has conducted individual interviews in the past. Both the participants and the interviewer were unknown to each other before the study. At the beginning of interview, participants were informed of the professional status of the interviewer and the scope of this study. Each participant was provided a AUD $50 gift card as a reimbursement for their time. All interview sessions were audio-recorded and transcribed verbatim. The median interview duration was 31 minutes (range, 22-50 minutes).

Interview transcripts were thematically analysed, following Braun and Clarke's six-step method of conducting thematic analyses [278]. This method was mainly chosen as it provides a clear step-by-step guide to start thematic analysis, and conduct it in a more deliberate and rigorous way. Transcripts were repeatedly read for familiarisation and data immersion. Following this, initial codes were generated from the data itself without using any *a priori* themes. The long list of initial codes were sorted and aggregated into potential themes. This was followed by review and refinement of themes, while discarding irrelevant themes and collapsing similar themes into an overarching theme. At this point, the themes were defined and further refined to be presentable for analysis. These finalised themes were then reported as results. SG independently coded the interview transcripts. The other two investigators KL and STRZ reviewed the codes to ensure concordance was reached. All the investigators agreed upon the final codes and subsequently generated themes. Qualitative data analysis software NVivo (QSR International Pty Ltd. Version 11.0) was used to facilitate the generation of preliminary codes and themes from the interview transcripts.

For this study, data saturation was considered as the point where no new codes could be generated from the interview transcripts. Data appeared to be saturated after the 15th interview as no new codes could be generated from the remaining three transcripts.

7.4. Results

Eighteen renal professionals comprising 12 nurses and six pharmacists participated in the individual interviews. The median age of participants was 44 years old (range, 25-60 years), and participants have a median of 11.5 years (range, 1-27 years) of

experience working in renal unit(s). Other demographic characteristics are presented in **Table 19**.

Table 19. Demographics of participants (n = 18)

Characteristics	**Category**	**Value**
Age, Years		44 (25-60)
	20-30	3 (16.7)
	31-40	4 (22.2)
	41-50	8 (44.4)
	≥ 51	3 (16.7)
Gender		
	Male	5 (27.8)
	Female	13 (72.2)
Level of education		
	Diploma	2 (11.1)
	Bachelors	7 (38.9)
	Graduate certificate	8 (44.4)
	Masters	1 (5.6)
Designation		
	Renal Pharmacist	6 (33.3)
	Registered Nurse	9 (50.0)
	Nurse Unit Manager	3 (16.7)
Experience in renal unit, Years		11.5 (1-27)
	1-10	8 (44.4)
	11-20	9 (50.0)
	≥ 21	1 (5.6)
Dialysis unit location		
	Metropolitan	12 (66.7)
	Rural	6 (33.3)

Note: Values expressed as number (percentage) or median (lower-upper limits of range).

The below sections describe the themes identified from the interviews, with a few key quotations from participants. A more detailed compilation of exemplar quotations have been included as **Appendix 20 and 21** to facilitate external confirmability auditing [279]. The following abbreviations are used for the section below when quoting participants: P = Pharmacist, N = Nurse, and the number indicates interview sequence.

7.4.1. Barriers to Assessing Medication Adherence

Seven themes were identified: prioritisation of resources, interplay between workload and available time, awareness and training deficits, concerns around practicality/suitability of adherence measures, communication of assessment services, patient participation, and trust. These themes have been categorised into three main categories: organisational, professional, and patient-level barriers. A summary of the barriers to assessing adherence is depicted in **Figure 14**, and further details regarding each theme is described in the following sections, under the relevant category headings.

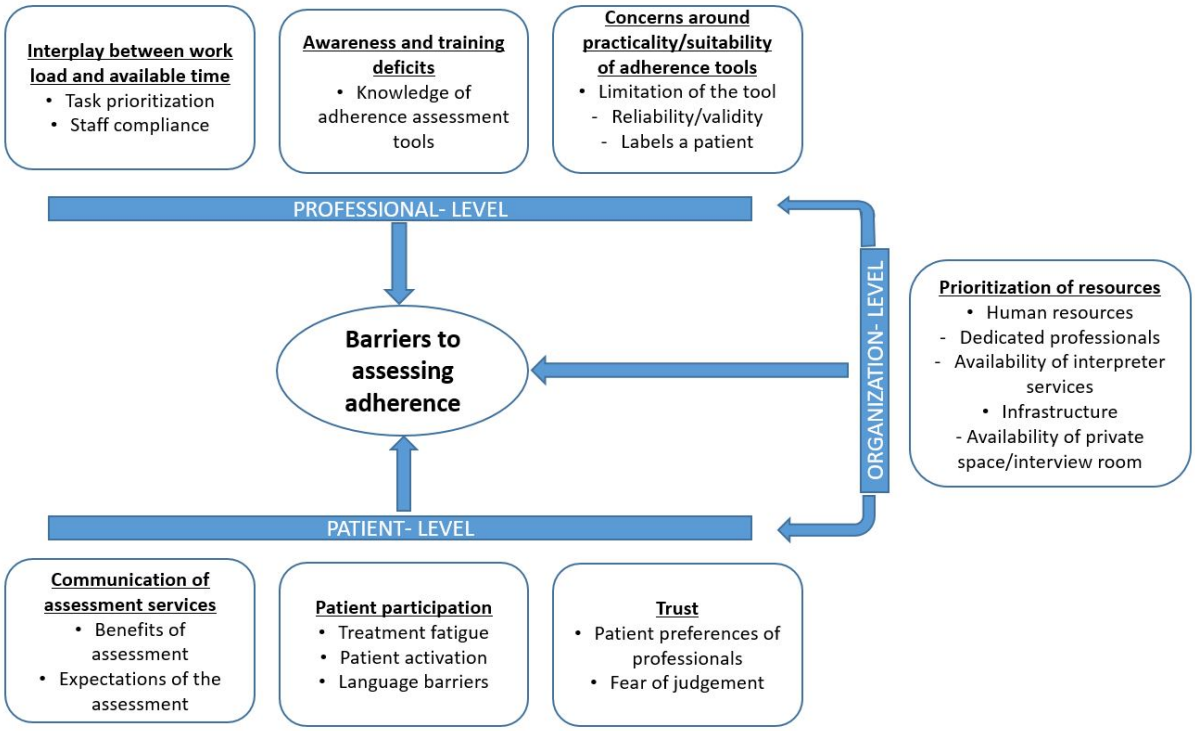

Figure 14. Barriers to assessing medication adherence in patients undergoing dialysis

7.4.1.1. Organisation-level

Theme: Prioritisation of resources

Interviews with participants revealed that a key barrier to assessing medication adherence was workplace prioritisation of resources:

> *It depends on the organisational priorities. If they are supportive of this [assessment process] or have a vested interest in this, or something like this, then the organisation is more likely to pursue this, but otherwise if they can't see any value in it, any direct dollar savings then it's unlikely to be pursued.* [P3, female, 50 years]

Specifically, based on our findings, it appeared that funding was a major factor for resource prioritisation. Participants expressed the need for having dedicated professionals, improved interpreter services for non-English speaking patients, and having a private space/interview room in the dialysis centres for conducting adherence assessment and promotion activities. Examples below:

> *[A] big limitation for conducting such activity [i.e. assessing adherence] is the absence of pharmacist in the unit. We wish to have a dedicated pharmacist to carry these activities.* [N7, female, 60 years]

> *[Interpreters are] not massively accessible. That is a barrier. Availability of an interpreter services is a barrier in the case of non-English speaking patients.* [P4, male, 45 years]

> *Privacy can be an issue because most of our patients sit very close to other patients and there is no way to go to the staff with anything privately.* [N11, female, 29 years]

7.4.1.2. Professional-level

Theme 1: Interplay between workload and available time

Amidst a variety of tasks performed while caring for patients undergoing dialysis, renal professionals may not have sufficient time to spend with their patients, and assessing medication adherence may not be a high priority when time is limited. Example:

> *If patients have health matters that are urgent, if they have been experiencing pain or having a lot of falls, or whatever that sounds like it's a new problem, the focus becomes on that, rather than other aspects like medications. Whereas, if*

the person is quite stable, probably there is more emphasis towards medicines. [P9, female, 34 years]

Staff compliance towards assessment services would also diminish due to task prioritisation and increased workload.

Staff participation may be poor. Unless it's really concerned with particular patients, or feel we need to monitor, but if we do it for everybody the work load is very high and some of the nurses won't be happy participating. They are already pre-occupied and may say oh! it's not our responsibility. [N15, male, 44 years]

Theme 2: Awareness and training deficits

Lack of awareness about formal adherence assessment tool was evident among the participants. An example:

I don't know any formal [assessment tools]. I've never heard about any official ones, I think it would be interesting to read about. [P4, male, 45 years]

However, one suggestion to address this barrier could be to provide training and education related to adherence assessments:

Nursing staff lacks necessary training and skills. I think definitely, there is room for improvement in relation to educating the nurses about medication on dialysis or all kidney failure patients. [N17, male, 53 years]

The above example highlights the gaps in training in relation to conducting adherence assessments.

Theme 3: Concerns around practicality/suitability of adherence tools

Participants identified several limitations of using formal assessment measures that would compromise identification of actual non-adherent behaviour. One perceived limitation is that of practicality and reliability of using methods such as validated questionnaires or objective pill counting:

> *It's not quite possible, it's not that easy to measure and absolutely quantify [adherence]. The only way you could do is you physically watch the patient for a week, you know, taking all their dosage. I don't think it's possible.* [P1, female, 32 years]

Some participants argued that measuring adherence might label a patient as being nonadherent.

> *I think it's good to get a general measure of adherence within patients, but I do sometimes find questionnaires label patients as being non-adherent and it's sort of taken as quite a nasty term.* [P5, female, 31 years]

7.4.1.3. Patient-level

Theme 1: Communication of assessment services

Participants reported the need to set expectations to ensure effective assessment of medication adherence. A reason for this, given by a participant, is because patients may perceive their privacy being invaded and would not participate:

> *It would depend on how it is presented, if it wouldn't be presented in a right way there would be patients who would become upset about why we are asking that*

question, and patients feeling of having their privacy invaded puts a lot of significant barriers of trust at the nurses. [N11, female, 29 years]

However, if the patients knows about the benefits of assessment, and what to expect of the assessment process, they would know why they are being asked certain questions and respond to assessment services:

I think most of the patients would be happy to answer the questions definitely, if they see the benefit from it that we care about the medicine they are taking. [N12, female, 32 years]

Theme 2: Patient participation

Several factors deterring patient participation in adherence assessment activities, based on the perspectives of renal professionals, were identified from our participants. These includes treatment fatigue from dialysis, patient activation (i.e. patient's motivation and perceived ability to contribute to their health management) [280], and language barriers especially with non-English speakers that would prevent patient from conveying their health-related issues to the health care team. Some examples:

Medical people oversee them and they have so many appointments, and if you ask them if they have any worries they will just say no. A lot of them, even if you offer review they go, no everything is fine, I actually don't need to see you. [P1, female, 32 years]

People do have free will. Even though we are trying to do the best to our patients, they still can go, 'I can't be bothered'. Then you have to go that point, well that's your decision not anybody else's. [P2, female, 47 years]

We had quite a few issues in our unit based on different cultural groups. We do have quite a few non-English speaking patients; basically they speak English but not enough to understand. [N11, female, 29 years]

Theme 3: Trust

Participants alluded to the concepts of trust and mistrust, and the impact of these concepts on the success of conducting a medication adherence assessment:

It's sad, I think some of them have mistrust about what we tell them, they don't trust that we are telling them the right thing or the truth about the medication what they require. [N6, male, 44 years]

They don't look at the nursing expertise, they also don't listen to suggestions [about taking medications] and, they say the doctors said do this way and they won't take on board with the nursing, also the lack of confidence in the nursing that we would know what they are talking about. [N18, female, 50 years]

Patients feel that they are going to be judged. That, they should by now know this information, why they are asking this pointless question, causing time wasting. [P3, female, 50 years]

As implied in the above quotations, it appears participants perceive that patients would prefer sharing their concerns with the professionals whom they trust the most, have a good rapport, and have no fear of judgement from their professionals regarding their adherence issues.

7.4.2. Considerations for Improving Adherence Assessment Practices

When asked to comment on the topic of improving adherence assessment practices, participants provided several suggestions. While some of the suggested activities coincide with current practice, participants emphasised that these activities should continue with routine dialysis care. A summary of considerations to improve adherence assessment practices is highlighted in **Table 20**.

Table 20. Considerations for improving adherence assessment practices

- **Formalisation of the adherence assessment process**
  - Formalise the process in hospital policy/procedures
- **Integration of the adherence assessment process and tools into routine**
  - Integrate adherence checklist into treatment sheet
- **Multidisciplinary support**
  - Partner with doctor and nursing staff
  - Liaising with interpreters and communication facilitators (e.g. formal/professional interpreters, informal/family interpreters, liaison with indigenous/aboriginal co-operatives)
- **Other specific activities**
  - Organise scheduled sessions for medication reviews (e.g. monthly review and reconciliation of medicines, patient report card review for blood levels)
  - Verification of objective evidence (e.g. direct observation of medicines, physical assessment, calling patient's local pharmacy, refill history, observing side effects of therapy)
  - Assess subjectively through patient communication (e.g. discussing patient concerns about medicines, non-judgemental questioning, maintaining good rapport and trusting relationships, being a good listener)

Underlying the suggested activities, three themes were identified: formalisation of the adherence assessment process, integration of the adherence assessment process and other adherence tools into routine, and using multidisciplinary support. Further details regarding each underlying theme is discussed in the following three sections.

Theme 1: Formalisation of assessment process

Participants commonly commented on the need to formalise the adherence assessment process in the dialysis settings, to prompt other renal professionals to perform adherence assessments as part of the care plan:

> *I think it might be good [to formalise assessment] because everybody then is following the same process. Staff know what to look for and what to ask. If you got a tool that it will prompt them to ask questions or prompt them to follow up on certain things.* [N18, female, 50 years]

Theme 2: Integration of assessment process and tools into routine

Participants proposed integrating an adherence checklist into their routine medication treatment sheets.

> *We could possibly have on a care plan a medication check and tick the boxes after conversation with the patients. Not so much the questionnaire, but just the prompt to have that conversation with the patients.* [N14, female, 49 years]

> *Well, our daily treatment sheet has, we already have some checklist we go through, sort of might be a simplest just adding up [adherence checklist], yeah, having any issues with your tablets or um, yeah.* [N8, female, 45 years]

Theme 3: Multidisciplinary support

An initiative for multidisciplinary support was advocated for a successful assessment of patient's adherence. An example:

> *I think we need to be involved in multidisciplinary approach, so we have support from our colleagues, so everybody is on the same page and support its initiatives and therefore the patients gets the consistent message that it's not just the pharmacists hounding them, but it's actually got value and purpose behind it.* [P3, female, 50 years]

Participants also expressed a need to liaise with communication facilitators such as formal or informal interpreters for non-English speaking patients, or indigenous liaison staffs in the case of indigenous or Aboriginal patients, as such patients would require support when making medical appointments and when communicating with their health professionals:

> *We use interpreters where necessary, if they are the patients with different languages.* [P1, female, 32 years]

> *We wait for their carers or family to come in who speak their language and we interpret via them.* [P3, female, 50 years]

> *For the indigenous, we have support from the Aboriginal liaison staffs so they can talk to her and help in medication management.* [N12, female, 32 years]

7.5. Discussion

We explored specialist renal pharmacists and nurses' perspectives on their challenges of assessing medication adherence in patients undergoing dialysis and ways by which adherence assessment practices could be improved in dialysis settings. Our study, for the first time, offers a number of insights into the organisational, professional, and patient-level factors that may impede adherence assessment activities in dialysis settings. In addition, this study also echoes some considerations such as formalisation and integration of the adherence assessment process into routine practice, and highlights the importance of multidisciplinary support required for a successful assessment of patient's medication-taking behaviour. Organisational and professional barriers identified from this study such as resource prioritisation in workplaces, time availability, and awareness and training deficits among health professionals corroborated with published studies [111, 245, 261, 281, 282]. Similarly, our study reiterates concerns surrounding practicality and suitability of adherence measures, which has been extensively discussed in studies on medication adherence [2, 10, 23, 283]. Sections hereafter will mainly discuss the unique findings of this study.

Our study revealed that, from the perspective of renal professionals, patients would prefer sharing their concerns with the professionals whom they trust the most, have no fear of judgement or risk of criticism, and have good patient-provider partnerships. Having a trustworthy relationship between patient-provider would influence assessment activity and can have a significant impact over patient's medication-taking behaviour [225]. While health professionals may have good intentions to assess adherence, if they fail to set expectations and identify benefits of assessing adherence, patients may turn hostile towards the assessment services and withdraw participation. Thus, communication can be a key to bridge the gap between patient-provider

relationships. Having good patient-physician communication can improve patient adherence, as supported by a meta-analysis study [282]. Communication can also be a key to patient activation, which involves providing necessary knowledge, skills and motivation to improve patient's ability to self-care and maintain their health conditions [280]. Patients have been found to follow recommended medical advice when they are in the higher stages of activation [284]. A recent systematic review has also highlighted the fact that increased patient activation scores are associated with decreased hospitalisation and emergency room utilisation in chronically ill patients, though the relationship with medication adherence were inconclusive [285]. Future research should explore the relationship between patient activation and its impact on medication adherence in patients with chronic diseases such as in ESKD patients undergoing dialysis.

Renal professionals emphasised on formalising the assessment process. This would normalise the activity, and patients would not feel their privacy invaded when inquired about their medication-taking behaviour rather would make themselves available for assessment. Similarly, participants proposed integrating adherence checklist into their routine care plan. Renal professionals can utilise any of the validated questions available in literature that non-judgementally asks patients about their medication adherence issues for example, *"I know it must be difficult to take all your medications regularly. How often do you miss taking them?"* Alternatively, patients may be asked about a particular medication, *"How often do you not take medication X?"* [1, 286] Prompting these questions may open up discussions pertaining to medication-related issues in patients undergoing dialysis. Past findings shows that disclosure of nonadherence through interviews and questionnaires have accurately represented patient's medication-taking behaviour [286-288]. However, it should be understood

that self-reported measures, though inexpensive and easy to use, comes with an inherent limitations such as recall bias and social desirability responses [289]. Moreover, accompanying challenges from organisation and professional's level while incorporating assessment services needs to be carefully considered. Due to the interplay between workload and available time, dialysis staff may seek to prioritize their routine task, which would diminish staff compliance towards the assessment services. More dedicated professionals may be required to carry out adherence assessment and promotion activities. However, organisations may have an altered priority for allocation of resources and finances that may discourage implementation and/or sustainability of such programs [111, 245, 281]. Further research is warranted to assess the feasibility and cost-effectiveness of implementing such programs in dialysis settings.

Our study has several implications for practice and research. As listed in **Table 20**, participants provided some essential and practical considerations to facilitate routine assessment process and promote adherence in dialysis settings. One of the key considerations was to conduct medication review and reconciliation on a regular basis. Medication reconciliation process confirms the accuracy of medication records with the patients/caregivers, whereas medication review involves in-depth analysis of medication regimen including appropriateness of therapy, dosing requirements, and monitoring of side effects and efficacy of the treatment [290]. As patients undergoing dialysis sees many prescribers, undergo frequent admissions, and are on multiple medications, this increases the risk for medication record discrepancies (MRDs) and medication-related problems (MRPs). On an average, 3.1 MRDs and 0.5 MRPs per patient has been observed in patients undergoing haemodialysis [290]. Thus, conducting a regular medication review and reconciliation by a dedicated professional

may facilitate early detection and intervention of medication-related problems in patients undergoing dialysis.

Participants also suggested verifying objective evidence while assessing adherence, for example, by calling patient's local pharmacy, checking refill history, or reviewing blood levels for certain drugs like phosphate binders. Pharmacy refill data can be a means to identify breaks between medication refills and help initiate patient dialogues for exploring medication-related issues. However, this method may only be effective within the closed pharmacy system, and does not necessarily provide direct evidence of medication administration by the patients [286]. In such cases, triangulation approach may be used whereby objective assessment may be carried out in conjunction with subjective methods like patient interviews or using self-reported questionnaires.

Participants from the present study also emphasised the role of multidisciplinary support for a successful assessment and adherence promotion. Renal professionals from disciplines such as medicine, pharmacy and nursing can work together and liaise with the interpreters or social workers for assessment services. Creating an opportunity for active patient involvement during therapeutic consultations with health professionals improves patient adherence to treatment [282]. Practice implications also extends to upgrading current renal professionals by providing trainings and skills necessary to assess and promote adherence. In addition, dialysis settings may upgrade current infrastructure needs by having a private space or interview room that may safeguard patients' privacy and allow exchange of dialogues in confidence. Proposed considerations will help inform the design and testing of new model of care that incorporates adherence assessment into routine practice for early identification of nonadherence issues in patients undergoing chronic dialysis treatment.

The present study is not without limitations. Focus group sessions were not attempted rather we relied on one-on-one interviews to generate insights based on personal perspectives that are unlikely to be shared during group discussions. As individual practices may vary between dialysis settings, the views expressed by the participants may not be generalisable to other settings; however, it is important to recognise that the aim of this study is to identify potential barriers and considerations for improving adherence assessment practices, and thus generalisability was not our primary purpose. In addition, the specialist renal pharmacists' viewpoints from Australian context may differ from other countries where pharmacists do not have specialised clinical roles. Further studies should be conducted to evaluate the applicability of our findings to wider populations. Nevertheless, given the diverse sample of renal professionals with varied years of experiences and levels of seniority, we believe our study captures a breadth of potential barriers and considerations for improving adherence assessment practices.

While the present study does have some limitations, its strength lie in the use of a recognised data analysis method proposed by Braun and Clark [278], which adds to the rigor of our findings. In addition, the conduct and reporting of this research was in accordance with the COREQ guideline [15]; this ensures that the details of the present study have been comprehensively reported, thereby facilitating dependability auditing [279], if required.

In conclusion, barriers to assessing adherence were identified at various organisational, professional, and patient levels. Current adherence assessment practices could be improved through formalisation and integration of the adherence assessment process into hospital policy/procedures, and overcoming existing barriers by appointing dedicated and trained professionals for conducting adherence

assessment and promotion activities in dialysis settings. Most importantly, renal professionals should opt for patient engagement where possible, frequently instigate dialogues and remain vigilant towards identifying patients' concerns related to medication that may help to resolve this significant issue of medication nonadherence in patients undergoing dialysis. Future research should consider designing and testing of new programs or model of care that incorporates adherence assessment into routine practice for early identification of medication nonadherence issues in patients undergoing chronic dialysis treatment.

Supplementary Material

Appendix 17. COREQ Checklist

Appendix 18. Interview Guide

Appendix 19. Barriers to assessing medication adherence in patients undergoing dialysis

Appendix 20. Considerations to improve adherence assessment practices in dialysis settings

CHAPTER EIGHT

8. CONCLUSION AND FUTURE DIRECTION

Patients often do not take their medications as prescribed, and this has been well documented in medical literature [1, 2, 16, 275]. Despite the fact that our understanding of the factors responsible for medication nonadherence has advanced during recent years, adherence assessment is still not a routine clinical practice. Increasing disease and medication regimen complexity can negatively affect patient adherence [197], and there is a paucity of data on the prevalence of, and factors responsible for, medication nonadherence in patients undergoing haemodialysis. As such, this thesis examined the potential predictors of medication adherence, explored current practices and barriers to assessing adherence, and identified strategies to improve adherence assessment practices in patients undergoing haemodialysis.

To adequately comprehend the issues surrounding medication nonadherence in the haemodialysis population, a systematic review study was conducted (as described in Chapter 2). Our data showed that between 12.5% and 98.6% of patients undergoing haemodialysis were nonadherent to their prescribed regimens. This is much higher in comparison to other chronic illnesses, such as diabetes (6.9% to 61.5%) [47], chronic psychiatric disorders (5.0% to 52.8%) [45], and other dialysis modalities, such as peritoneal dialysis (3.9% to 43.0%) [25].

We observed that a variety of adherence measures are utilised across studies, which has resulted in the reporting of this wide-ranging prevalence pattern. Given the absence of a unified standardised approach to measuring medication adherence, this

systematic review highlights the necessity of a consensus on defining and assessing adherence in patients taking long-term medications. An initiative to standardise the taxonomy of adherence was attempted by the International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) special interest group [291], however, their definitions were impelled by assessment methods related to refill data that would only deliver a limited view of adherence. Most recently, the European consensus meeting on the taxonomy and terminology of patient compliance has proposed a new taxonomy for describing and defining adherence to medications with an approach that remains independent of any assessment methods [26].

The findings of this systematic review further enhanced our understanding of the potential risk factors associated with medication nonadherence in patients undergoing haemodialysis. A number of patient-, disease-, and medication-related factors contributing to nonadherence were identified, which may help healthcare professionals to be more strategic in terms of making therapeutic decisions and recommendations based on the risk factors and their influence over patients' medication-taking behaviour. Taking account of patients' concerns and beliefs regarding medication can improve the quality of prescribing, help clinicians involve patients in therapeutic decisions, and support optimal adherence to prescribed therapy [200].

Although patients undergoing haemodialysis are often prescribed with complex medication regimens [203], this systematic review could only identify one article that investigated medication regimen complexity as a potential predictor of adherence [150]. Furthermore, the study defined regimen complexity based on frequency and dosage schedule instead of using a validated measure [201]. Therefore, to address the role of medication regimen complexity in determining nonadherence in patients

undergoing haemodialysis, we felt there was a need for a more rigorous study design that uses a validated tool, such as the medication regimen complexity index (MRCI), to determine the association between regimen complexity and adherence in patients undergoing haemodialysis.

The second study (described in Chapter 3) was instrumental in finding the actual association between medication regimen complexity and adherence in patients undergoing haemodialysis. An unanticipated association between regimen complexity and adherence was observed where older patients undergoing haemodialysis with high comorbidity and higher regimen complexity scores were actually more adherent to their prescribed regimens compared to their younger counterparts.

Adherence is a dynamic phenomenon, and it is often the net result of an interplay of a number of factors. The negative consequences of poor adherence can be more severe in patients undergoing haemodialysis with increasing comorbidities and regimen complexity. Importantly, younger patients with less complex regimens and fewer comorbidities may not realise the negative consequences of nonadherence, and may not realise the importance of adhering to their prescribed medicines.

Similar to our findings, other studies have also found older patients undergoing haemodialysis to be more adherent to medicines than their younger counterparts [11, 150]. One reason may be that older patients with multiple comorbidities are more concerned about mortality and prefer structured lives, and therefore adhere to their medication therapy despite increasing polypharmacy and associated regimen complexity [11]. Furthermore, older patients may also be more health conscious and receive more support and attention from family members and healthcare teams, which could potentially help them adhere to their medication [150, 292].

This study signifies the need to support younger patients undergoing dialysis during their early adjustment to haemodialysis prescriptions [220]. As an exploratory single-centric study conducted with a small sample of patients undergoing haemodialysis, however, the study findings may not be generalisable, and therefore need to be confirmed through larger prospective observational studies. Nonetheless, the unanticipated findings of this study necessitate further exploration of patients' perspectives on their medication-taking behaviour, and of why such discrepant findings were observed.

The third study (described in Chapter 4) was a follow-up qualitative inquiry that aimed to explore the differential perspectives on medication-taking behaviour shown by adherent and nonadherent patients undergoing haemodialysis. The findings from this qualitative exploration identified a number of factors that led to nonadherence behaviour in patients undergoing haemodialysis. Some of the unique aspects highlighted in this study include patients reporting their poor interaction with healthcare professionals, which led to mistrust of the healthcare providers' recommendations, and the making of collateral arrangements by the patients regarding their treatment and medications, all of which fosters nonadherence behaviour. This suggests that improving patient adherence may require creating an opportunity for active patient participation during therapeutic consultations with healthcare providers.

Developing a trustworthy relationship between patients and providers can have a significant impact on patients' medication-taking behaviour [225]. Furthermore, having good patient-physician communication has been found to improve adherence, as suggested by a meta-analysis study [282]. Therefore, renal healthcare professionals should routinely instigate dialogues and encourage patients to volunteer information concerning their current medicines, readiness to start their new therapy,

changes in dose or dosage requirements, and concerns related to medication safety and side effects from therapy. This would lead to the early identification of any issues pertaining to nonadherence behaviour, and preventive measures could be taken pro-actively.

Understanding renal healthcare professionals' perceptions and practices of assessing adherence was equally important for having an unbiased insight into the problem of nonadherence, and for finding solutions to resolve the significant issue of nonadherence in patients undergoing haemodialysis. Hence, the fourth study was designed to comprise cross-sectional surveys (described in Chapters 5 and 6), and a follow-up qualitative study of renal professionals (described in Chapter 7).

In the absence of an existing survey tool, a new survey instrument was developed and pilot-tested in specialist renal pharmacists (Chapter 5) and renal nurses' cohorts (Chapter 6). As no prior tools were available, we considered developing an instrument that would capture various perception domains and which consisted of five individual psychometric scales capable of measuring perceived prevalence, contributors, effective methods, barriers, and confidence to assess adherence, together with a current practices questionnaire.

These tools can be used in practice settings as part of any quality initiative program targeting nonadherence. For instance, the Pharmacy Guild of Australia (PGA) has initiated the Medication Adherence Programs (MAP) aimed at improving patients' adherence to medicines [293]. The PGA has recently introduced a new software program called 'Guildcare' that analyses pharmacies' dispense database to calculate patient's 'MedsIndex' score [293]. Patients with sufficiently low MedsIndex scores are

invited to participate in the MAP, where they are provided with a range of services focused on improving adherence.

The MAP align with the Australian government's National E-Health Strategy and the key objectives of Australia's continuing health reform agenda on Quality Use of Medicines (QUM), and is designed to assist pharmacists in assessing patient adherence. Whereas the development of a survey instrument such as ours can facilitate the understanding of healthcare professionals' perceptions and actual practices of assessing and promoting adherence in routine clinical practices.

Findings from these surveys and the follow-up qualitative inquiry of renal professionals has, for the first time, offered insights into the current adherence assessment practices in dialysis settings, and suggest that the practices are suboptimal and that the established methods to screen patient adherence are underutilised. Furthermore, the majority of the participants acknowledged that having a dedicated pharmacist would be effective in promoting adherence activities, but that these services were mostly unavailable in dialysis settings.

Moreover, participants identified several barriers to assessing adherence at organisational, professional, and patient levels that need urgent attention in order to improve adherence assessment practices in dialysis settings. As more dedicated professionals may be required to conduct adherence assessments and promotion activities, the feasibility and cost-effectiveness of implementing such programs may warrant further research in the future.

8.1. Practice Implications

Patients alone cannot be blamed for not adhering to their prescribed regimens; both healthcare providers and the healthcare system should also bear some responsibility and play their part in improving adherence. As medication nonadherence is highly prevalent among patients undergoing haemodialysis, improving it may require creating an opportunity for an open discussion between patients and healthcare professionals. There is a need for broader recognition of this often undetected and undertreated problem in routine clinical practices. A practical first step to recognise nonadherence is to include it in the routine dialysis sessions alongside the measurements of vital signs, e.g. pulse monitoring, and temperature or blood pressure measurements.

Although self-reporting may seem to be an insensitive measure [27], the routine instigation of dialogues may encourage patients to volunteer information concerning their medicines. Patients may be able to provide useful insights into their readiness to start a new therapy, changes in dose or dosage requirements, and any concerns regarding medication safety and side effects. As adherence measures differ in their definition and assessment methods, the use of multiple measures may be helpful in identifying nonadherence and assuring consistent results [33]. As such, self-reporting may be supplemented with objective measures, such as the monitoring of blood levels [33] and, a history of patient medication purchasing behaviour [294].

Recognition of medication nonadherence in patients will allow healthcare providers and patients to make a collaborative effort in developing patient-specific tailored solutions to address the problem. Simple, evidence-based strategies can then be offered to patients, such as reducing daily pill burden, organising dosage administration aids for forgetful patients, conducting motivational patient-interviews, or outlining the rationale and therapeutic need of a prescribed regimen [295].

As access to medicines, and issues surrounding continuity of care, can contribute to unintentional nonadherence [232], access to dialysis centre-specific professional medical and pharmaceutical services may be improved by increasing focus on adherence assessment and promotion activities, and on delivering educational support to the patients. Practice implications also extend to the improvement of current renal professionals by providing the training and skills necessary to assess and promote adherence in patients undergoing dialysis.

8.2. Limitations of the research

The studies reported in this thesis are mainly aimed at understanding the determinants of medication adherence in patients undergoing haemodialysis, and how adherence is measured within Australian dialysis settings. As such, examining the clinical outcomes and consequences of medication nonadherence was beyond the scope of this research. The patients undergoing haemodialysis were sourced from a single outpatient dialysis centre, which may compromise the generalisability of the findings.

The use of self-reported questionnaires and data from patient qualitative interviews can be susceptible to recall bias and social desirability, resulting in an overestimation of actual medication-taking behaviour [32]. Due to the cross-sectional nature of this study, the adherence behaviour reported may be influenced by the reverse causation bias [206]. Also, during the cross-sectional survey of the renal healthcare professionals, various recruitment strategies were used to gather responses from the renal physicians. Due to extremely poor representation, however, the renal physician survey responses were excluded from the analysis. Poor physician responses have been commonly observed in survey research [110, 250].

8.3. Future direction

Several prospects for future research arose from this body of work:

- The study described in Chapter 3 was exploratory in nature, and was conducted in a single centre with a small sample of patients undergoing haemodialysis. Future research should aim to recruit a larger sample of patients, and should use objective measures of adherence suitable for all patients and reflecting all medications (e.g. medication possession ratio), to assess the exploratory findings of this study. Furthermore, future studies should explore the potential use of the triangulation method, whereby subjective and objective adherence assessment measures supplement each other in determining actual patient adherence to medication.
- The qualitative study described in Chapter 4 was limited to English-speaking patients only. Future work should aim to include a more diverse cohort of patients undergoing haemodialysis, including those from indigenous and aboriginal backgrounds, to improve the generalisability of the findings.
- Due to poor representation from renal doctors during the cross-sectional survey study, the understanding of renal professionals' perception and practices of assessing adherence was limited to renal pharmacists (Chapter 5) and renal nurses (Chapter 6). Future research should aim to comprehend renal doctors' perspectives on this issue.
- In the absence of a validated instrument that measures renal professionals' perceptions and practices of assessing adherence, a survey instrument was developed and piloted (Chapters 5 and 6). This survey instrument has good reliability and future studies can utilise this survey instrument when conducting larger nationwide surveys of renal professionals.

- The considerations proposed to improve the adherence assessment practices of the renal professionals (reported in Chapter 7) can help inform the design and testing of new models of care that incorporates adherence assessment into routine practice for the early identification of nonadherence issues in patients undergoing chronic dialysis treatment.

8.4. Conclusion

This thesis has addressed important gaps in our understanding of the factors affecting medication adherence in patients undergoing haemodialysis, and of the current adherence assessment practices in Australian dialysis settings. There is a need for broader recognition of this often undetected and undertreated problem in routine clinical practices. Improving medication adherence among patients undergoing haemodialysis may require creating an opportunity for an open discussion between patient and healthcare professionals. This may be the very first step in the right direction towards assessment and promotion of medication adherence in patients undergoing dialysis.

In addition, current adherence assessment practices could be improved through their formalisation and integration into hospital policies/procedures (e.g. by integrating an adherence checklist into the treatment sheet for routine assessment). Although it is easier said than done, appointing a dedicated and trained healthcare professional to measure adherence is another key initiative that may improve medication adherence among patients undergoing dialysis.

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APPENDICES

Appendix 1. PRISMA Checklist

Section/topic	#	Checklist item	Reported in section
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title Page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Study selection
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Study selection
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Data source and search strategy
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S2 Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Study selection
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Data extraction and analysis
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Data extraction and analysis
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Quality assessment
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Data extraction and analysis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Data extraction and analysis

Section/topic	#	Checklist item	Reported in section
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Data extraction and analysis
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Data extraction and analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Description of included studies
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Study quality
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1, Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Study quality
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Perceived barriers
DISCUSSION			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusion
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: **www.prisma-statement.org**.

Appendix 2. Electronic search strategy, Systematic Review

ID	Query
PubMed Search Strategy	
#1	(((((((hemodialysis[MeSH Terms]) OR hemodialysis, home[MeSH Terms]) OR hemodialysis unit, hospital[MeSH Terms]) OR therapy, renal replacement[MeSH Terms]) OR disease, end stage kidney[MeSH Terms]) OR chronic renal failure[MeSH Terms]) OR chronic renal insufficiency[MeSH Terms]) OR chronic kidney failure[MeSH Terms]) OR chronic kidney insufficiency[MeSH Terms]
	AND
#2	((((adherence, medication[MeSH Terms]) OR adherence, patient[MeSH Terms]) OR compliance, medication[MeSH Terms]) OR compliance, patient[MeSH Terms]) OR concordance
	AND
#3	((((medication*) OR regimen*) OR schedule*)) OR ((session*) OR exchange*)
Embase Search Strategy	
#1	(('hemodialysis'/exp/mj OR 'hemodialysis') OR ('end stage renal disease'/exp/mj OR 'end stage renal disease') OR ('chronic kidney failure'/exp/mj OR 'chronic kidney failure') OR ('renal replacement therapy-dependent renal disease'/exp/mj OR 'renal replacement therapy-dependent renal disease'))
	AND
#2	(('drug therapy'/exp OR 'drug therapy') OR ('drug'/exp/mj OR 'drug') OR ('drug dose regimen'/exp OR 'drug dose regimen'))
	AND
#3	(('medication compliance'/exp OR 'medication compliance') OR 'concordance')
CINAHL Search Strategy	
S1	(MH "Hemodialysis") OR (MM "Renal Replacement Therapy+") OR (MM "Kidney Failure, Chronic+") OR (MM "Renal Insufficiency, Chronic+")
	AND
S2	(MM "Medication Compliance") OR (MM "Patient Compliance+") OR "concordance"
	AND
S3	"medication" OR "drug" OR (MH "Medication Regimen (Omaha)") OR "regimen" OR (MM "Drug Administration Schedule")
PsycInfo Search Strategy	
S1	hemodialysis OR (hemodialysis unit) OR (renal replacement therapy) OR (end stage kidney disease) OR (end stage kidney failure) OR (chronic renal failure) OR (chronic kidney failure) OR (chronic kidney insufficiency) OR (chronic renal insufficiency)
	AND
S2	adherence OR (medication adherence) OR (patient adherence) OR compliance OR (medication compliance) OR (patient compliance) OR concordance OR (patient concordance)
	AND

S3	medication* OR drug* OR regimen* OR schedule*
Cochrane Search Strategy	
#1	MeSH descriptor: [Renal Dialysis] this term only
#2	MeSH descriptor: [Hemodialysis Units, Hospital] explode all trees
#3	MeSH descriptor: [Hemodialysis, Home] 1 tree(s) exploded
#4	MeSH descriptor: [Renal Replacement Therapy] this term only
#5	MeSH descriptor: [Kidney Failure, Chronic] this term only
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Medication Adherence] explode all trees
#8	MeSH descriptor: [Patient Compliance] this term only
#9	"concordance":ti,ab,kw (Word variations have been searched)
#10	#7 or #8 or #9
#11	"medication":ti,ab,kw (Word variations have been searched)
#12	"drug":ti,ab,kw (Word variations have been searched)
#13	"regimen":ti,ab,kw (Word variations have been searched)
#14	"schedule":ti,ab,kw (Word variations have been searched)
#15	#11 or #12 or #13 or #14
#16	#6 and #10 and #15

Appendix 3. Patient Medication History Interview Questions

A. ALLERGIES

1. Do you have an allergy to or avoid any medications due to side effects?
2. What type of reaction do you have?

B. PRESCRIPTION MEDICATIONS

1. What prescription medications do you take on a regular basis?
2. When do you take them?

C. NON-PRESCRIPTION MEDICATIONS

1. What non-prescription over-the-counter (OTC) medications do you take on a regular basis?
2. When do you take them?

D. HERBALS/ COMPLEMENTARY AND ALTERNATIVE/ SUPPLEMENTS/ VITAMINS

1. What herbal, natural or homeopathic remedies do you take?
2. What vitamins or minerals do you take?
3. When do you take them?
4. How do you take them?

E. ADDITIONAL QUESTIONS

1. **Do you use any:**
   - Eye drops
   - Nose sprays
   - Puffer (Inhalers)
   - Medicated lotions or creams
   - Medicated patches

2. **Do you receive any:**
   - Needles (injections)
   - Samples from the doctor's office

3. **Do you take any medication on a regular basis:**
   - For sleep
   - For your stomach
   - For your bowels
   - For pain

4. **Do you take any medication on an irregular basis:**
   - Weekly/ fortnightly/ monthly

Appendix 4. Patient Self-reported Questionnaires

Health outcome measure:

Patient's health outcome measure will be assessed using EQ-5D-5L, a standardised instrument developed by EuroQol Group. The EQ-5D-5L descriptive system is composed of 5 dimensions: mobility, self-care, usual activities, pain/ discomfort, and anxiety/ depression. Each of these domains have 5 levels: no problem, slight problems, moderate problems, severe problems, and extreme problems. The decision results in a 1- digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5- digit number describing the respondent's health state.

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems with walking around ❑

I have slight problems with walking around ❑

I have moderate problems with walking around ❑

I have severe problems with walking around ❑

I am unable to walk around ❑

PERSONAL CARE

I have no problems with washing or dressing myself ❑

I have slight problems with washing or dressing myself ❑

I have moderate problems with washing or dressing myself ❑

I have severe problems with washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

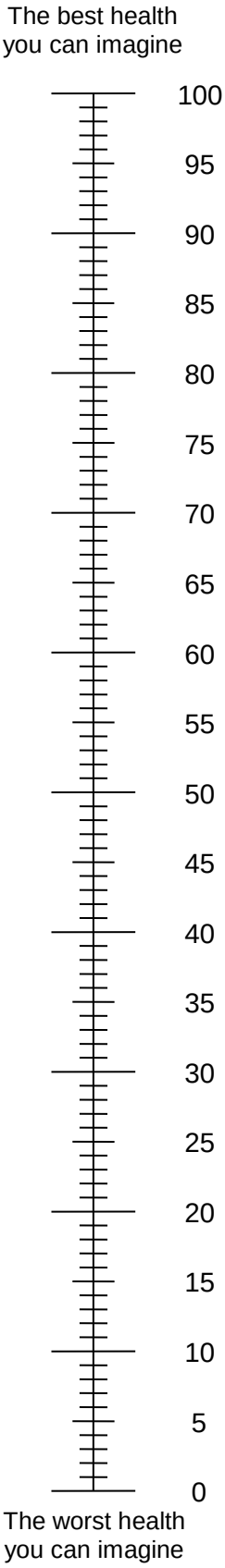
I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Self-reported adherence:

Please answer **Yes/ No**:

a. Do you ever forget to take your medicine? _____
b. Are you careless at times about taking your medicine? _____
c. When you feel better do you sometimes stop taking your medicine? _____
d. Sometimes if you feel worse when you take your medicine, do you stop taking it? _____

Perceived burden of medication administration:

Please score between **1 and 5**.

1 = Not at all bothered

2 = Slightly bothered

3 = Moderately bothered

4 = Severely bothered

5 = Extremely bothered

How much are you bothered by the:

a. Number of medication prescribed? _____
b. Size of the pills? _____
c. Adverse effects of medication? _____
d. Number of times medicines should be administered during the day? _____
e. Need to take medicines at work or in social contexts? _____
f. Need to drink water in order to take medication? _____

Appendix 5. Data collection form

Patient ID	Patient Name	ALLERGIES & ADVERSE DRUG REACTIONS (ADR)	
		Drug (or Other)	Reaction/ Date
Age	Gender		
Time of ESKD	Education	Employment	
Marital S	Living arrangement	Smoking	Alcohol

CHECKLIST: Ask the patient about the following : (✓)

- ☐ prescription medicines
- ☐ over the counter medicines
- ☐ complementary and alternative medicines including vitamins and nutritional supplements
- ☐ topical preparations (patches, creams, ointments, etc)
- ☐ eye, ear, nose and throat drops/medications
- ☐ inhaled medications
- ☐ injections, implants, pessaries, suppositories
- ☐ sleeping tablets
- ☐ oral contraceptives, hormone replacement therapy
- ☐ GI drugs (reflux, heartburn, constipation, diarrhoea)
- ☐ analgesics
- ☐ other peoples tablets
- ☐ social and recreational drugs

Current medication (Generic/ Trade name)	Dosage form (Strength)	Dosing frequency (How often)	Additional dir (With food etc.)	Current comorbid conditions (✓)	
					Heart problems (CAD, CHF)
					Vascular disease (PAD)
					High blood pressure
					Diabetes (W/Wo EOD: retino, neuro, nephropathy)
					Thyroid problems
					Muscle/ bone disorders
					Lung problems
					Liver disease
					Bleeding problems
					Stomach problems (Ulcer)
					Vision problems
					Infections
					Arthritis
					Cancer
					Neurological problems
					Mental health issues

Appendix 6. Medication Regimen Complexity Index, MRCI

MEDICATION REGIMEN COMPLEXITY INDEX

Patient ID: ----------
Total no. of medications (including prn/sos medications): ----------

Instructions

1. MRCI applies only to prescribed medications. All entries are to be made only based on information on the label or drug chart (at the time of dispensing or discharge). No assumptions are to be made based on clinical judgement.
2. There are three sections in the scale. Complete each section before proceeding to the next. At the end, add the scores for the three sections to give the MRCI.
3. If the same medication (same brand and same dosage form) is present more than once in different strengths in a regimen (e.g. Marevan 5mg, 3mg and 1 mg mdu), it is still considered as one medication.
4. In cases where the dosage is optional, choose the dosing instruction with the smallest dose/frequency. (e.g. Ventolin MDI 1-2 puffs, 2-3 times daily will get weightings for 'metered dose inhalers', 'variable dose' and 'twice daily'; but not for 'multiple units at one time')
5. In certain cases the dosing frequency needs to be calculated (e.g. Ranitidine 1mane and 1nocte is 1twice daily)
6. It is possible that with certain 'use as directed' instructions, the regimen will not get a score under dosing frequency (e.g. Prednisolone 5mg mdu)
7. If there is more than one dosing frequency direction, they should be scored for all the dosing frequency directions (e.g. Ventolin MDI 2 puffs bd and prn, will get scores for 'metered dose inhalers', 'multiple units at one time', 'twice daily' as well as 'prn')
8. Instances where two or more medications are mutually exclusive, they need to be scored twice or more as prn with the recommended dosing frequency (e.g. Ventolin MDI or Ventolin nebuliser twice daily will get scores for both 'metered dose inhalers' and 'nebuliser' under dosage forms, but needs to be scored two times for 'twice daily prn')
9. In cases where there is no matching option, choose the closest option (e.g. six times daily could be considered as 'q4h')

A) Circle the weighting corresponding to each dosage form (ONCE ONLY) present in the regimen.

Dosage Forms		Weighting
ORAL	Capsules/Tablets	1
	Gargles/Mouthwashes	2
	Gums/Lozenges	2
	Liquids	2
	Powders/Granules	2
	Sublingual sprays/tabs	2
TOPICAL	Creams/Gels/Ointments	2
	Dressings	3
	Paints/Solutions	2
	Pastes	3
	Patches	2
	Sprays	1
EAR, EYE & NOSE	Ear drops/creams/ointments	3
	Eye drops	3
	Eye gels/ointments	3
	Nasal drops/cream/ointment	3
	Nasal spray	2
INHALATION	Accuhalers	3
	Aerolizers	3
	Metered dose inhalers	4
	Nebuliser	5
	Oxygen/Concentrator	3
	Turbuhalers	3
	Other DPIs	3
OTHERS	Dialysate	5
	Enemas	2
	Injections: Prefilled	3
	Ampoules/Vials	4
	Pessaries	3
	Patient controlled analgesia	2
	Suppositories	2
	Vaginal creams	2
	Total for Section A	

DPI = dry powder inhaler; MDI = metered- dose inhaler.

Medication Regimen Complexity Index (MRCI) (continued)

B) For each medication in the regimen tick a box [√] corresponding to the dosing frequency. Then, add the no. of [√] in each category and multiply by the assigned weighting. In cases where there is no exact option, choose the best option.

Dosing Frequency	Medications	Total	Weighting	Weighting × No. of medications
Once daily			1	
Once daily prn			0.5	
Twice daily			2	
Twice daily prn			1	
Three times daily			3	
Three times daily prn			1.5	
Four times daily			4	
Four times daily prn			2	
q 12h			2.5	
q 12h prn			1.5	
q 8h			3.5	
q 8h prn			2	
q 6h			4.5	
q 6h prn			2.5	
q 4h			6.5	
q 4h prn			3.5	
q 2h			12.5	
q 2h prn			6.5	
prn/sos			0.5	
On alternate days or less frequently			2	
Oxygen prn			1	
Oxygen <15hrs			2	
Oxygen >15hrs			3	
			Total for Section B	

C) Tick a box [√] corresponding to the additional directions, if present in the regimen. Then, add the no. of [√] in each category and multiply by the assigned weighting.

Additional Directions	Medications	Total	Weighting	Weighting × No. of medications
Break or crush tablet			1	
Dissolve tablet/powder			1	
Multiple units at one time (e.g. 2 tabs, 2 puffs)			1	
Variable dose (e.g. 1-2 caps, 2-3 puffs)			1	
Take/use at specified time/s (e.g. mane, nocte, 8 AM)			1	
Relation to food (e.g. pc, ac, with food)			1	
Take with specific fluid			1	
Take/use as directed			2	
Tapering/increasing dose			2	
Alternating dose (e.g. one mane & two nocte, one/ two on alternate days)			2	
			Total for Section C	

Medication Regimen Complexity = Total (A) + Total (B) + Total (C)=

DPI = dry powder inhaler; MDI = metered- dose inhaler.

Appendix 7. COREQ Checklist: Patient Interview

No. Item	Guide questions/ description	Reported in section/ remarks
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Interviewer/ facilitator	Which author/s conducted the interview or focus group?	Research team and reflexivity
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	PhD
3. Occupation	What was their occupation at the time of the study?	Research team and reflexivity
4. Gender	Was the researcher male or female?	Male
5. Experience and training	What experience or training did the researcher have?	SG was trained for pharmacists Home Medicines Review on medication history taking and collating medication-related information and provided one-on-one coaching to interview complex patients by the hospital pharmacist.
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	Research team and reflexivity
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	Research team and reflexivity. Data collection.
8. Interviewer characteristics	What characteristics were reported about the interviewer/ facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	SG discussed prior literature on Medication nonadherence in patients undergoing haemodialysis, and how little is known about the patients' perspectives in outpatient dialysis setting.
Domain 2: Study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	Data collection and analysis
Participant selection		
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	Participants
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	Participants
12. Sample size	How many participants were in the study?	Participants
13. Non-participation	How many people refused to participate or dropped out? Reasons?	Participants
Setting		

No. Item	Guide questions/ description	Reported in section/ remarks
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	Data collection and analysis
15. Presence of nonparticipants	Was anyone else present besides the participants and researchers?	No
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	Participants
Data collection		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Data collection and analysis. Appendix 2.
18. Repeat interviews	Were repeat interviews carried out? If yes, how many?	Not conducted
19. Audio/ visual recording	Did the research use audio or visual recording to collect the data?	Data collection and analysis
20. Field notes	Were field notes made during and/or after the interview or focus group?	Data collection and analysis
21. Duration	What was the duration of the interviews or focus group?	Data collection and analysis
22. Data saturation	Was data saturation discussed?	Data collection and analysis
23. Transcripts returned	Were transcripts returned to participants for comment and/ or correction?	No
Domain 3: Analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	Data collection and analysis
25. Description of the coding tree	Did authors provide a description of the coding tree?	No. Intermediate documentation is available upon request.
26. Derivation of themes	Were themes identified in advance or derived from the data?	Data collection and analysis
27. Software	What software, if applicable, was used to manage the data?	N/A
28. Participant checking	Did participants provide feedback on the findings?	No
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes/ findings? Was each quotation identified? e.g. participant number	Results. Table 2. Appendix 3.
30. Data and findings consistent	Was there consistency between the data presented and the findings?	Yes
31. Clarity of major themes	Were major themes clearly presented in the findings?	Results
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Results

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357.

Appendix 8. Interview guide: Patient Interview

Opening statement for the participants:

Thank you for participating in this study. Before we begin, I'd like to summarise the structure of this session. At first, I'll be discussing with you about the medications you are currently taking for all your health conditions that may include prescription, non-prescription, and complementary or alternative medicines such as herbal medicines. Following that, I'd like to hear some of your experiences of taking medicines. I also have some questions discussing about your health conditions. These questions will give you an opportunity to talk about your medicines, how well you feel they work, side effects, and so on. This interview should take no more than 30 minutes. Your participation will be completely voluntary and you may prefer not to answer any of the questions if you are not willing to. I'd like to audiotape this conversation for future reference however, all your responses will be kept confidential and will not affect your medical care in any way. Do you have any questions or concerns you'd like to discuss before we begin?

If yes: (give answer)

If no: (begin interview)

Questions relating to experiences of taking medicines:

1. How do you **feel about** your medicines?
2. How are your medicines **helping** your illness?
3. How do your medicines **affect your** life?
4. On what way does your medicines affect your **family and social** life?
5. What are the things you **don't like** about taking your medicines?
6. What is the **most challenging** part of taking your medicines?
7. What **situations** make it difficult for you to take your medicines?
8. What are the things that **helps you** to take your medicines?
9. In what situations you **feel easy** taking your medicines?
10. What are the **problems** you face while taking your medicines?
11. What are the **ways to fix** any of the medication related problems you face?
12. How do you seek help for the **management** of specific symptoms?
13. Where do you go or whom do you **seek for help** to talk about your medicines?
14. When you **see your doctor**, how does the session usually go?
15. What are the **skills** that you have adapted for taking your medicines?
16. How do you manage your **expenses** for medication?

References:

1. Ogedegbe G et al. Barriers and facilitators of medication adherence in hypertensive African Americans: a qualitative study. *Ethn Dis*. 2004;14(1):3-12.
2. Williams AF et al. Adherence to multiple prescribed medications in diabetic kidney disease: a qualitative study of consumers' and health professionals' perspectives. *Int J Nurs Stud*. 2008;45(12):1742-1756.

Appendix 9. Summary of interpretation of themes with exemplar quotes: Patient Interview

Themes based on WHO taxonomy	**Exemplar quotes**
Patient-related factors[μ]	
Knowledge and beliefs	
- Lack of understanding about medicines	*"Well, I just don't know what some of them are for."* (P1, male, 53 years, PSR NAD)
	"I don't know what's really important and… if you missed [medication] once or twice it wouldn't matter, I've no idea." (P5, female, 58 years, PSR NAD)
	"As far vitamins are no much point for me because it all gets dialysed out of here [pointing to the dialysis machine]." (P8, male, 71 years, PSR NAD)
- Lack of benefit	*"I don't know if they doing any good? […] I thought well, you know, I am taking all this in the morning, um… are they doing any good? I don't know."* (P5, female, 58 years, PSR NAD)
- Relative importance	*"I think blood pressure one is important. Yes, I think that is important to keep my blood pressure down…"* (P6, female, 74 years, PSR NAD)
	"Except for the, ah, Atorvastatin, I'm fairly happy with my medicines." (P6, female, 74 years, PSR NAD)
- Perceived need	*"I think, you got a put in your head you got a pills because they are trying to help you, so you take them."* (P11, male, 84 years, PSR AD)
	"There's something to do with my kidney and that. […] it's not working very well. If I started not taking them, I could for been… you know in trouble. They all they are for a reason. Yeah." (P15, male, 78 years, PSR AD)
	"I always take them. If I stop taking them, I don't do anything, I can't move. I just stiffen up like this and that's it." (P16, male, 65 years, PSR AD)
- Perceived effectiveness	*"I put myself on that [medicine] because I didn't have any arthritis or anything before I started [dialysis] and all of a sudden my fingers going, and I put it on that now for a month and it stopped the pain…"* (P12, female, 80 years, PSR AD)
- Safety concerns	*"I stopped taking them [phosphate binders]. You know, it got me there badly, it got me suffer physically… I mean it must be that one [phosphate binders] because all the other one's are fine. I haven't vomited for ages, and I'm very careful about the diet."* (P5, female, 58 years, PSR NAD)
	"There's one medicine that is a statin which I'm very unhappy about. It's Atorvastatin. And, I'm unhappy about that… because they… they, ah, studies have shown that there are lots of side effects of that." (P6, female, 74 years, PSR NAD)
Awareness	
- Consequences of nonadherence and motivation to live	*"I don't know how much longer I got to live. But I want to get up to 80. If I become 80, that will be the longest lived in all our family. And if I make 80… I'm the champion."* (P15, male, 78 years, PSR AD)
	"Oh, it [medicines] doesn't worry me. Its keeping me alive, this medicines keeping me alive so, I do whatever I've to. If I don't take them I'm probably dead." (P12, female, 80 years, PSR AD)
	"If you don't [take] you won't breathe." (P20, male, 80 years, PSR AD)
	"doesn't worry me because they are keeping me alive. Like the treatments keep me alive, the medicines are keeping me alive." (P21, male, 84 years, PSR AD)

Themes based on WHO taxonomy	Exemplar quotes
	"If I don't take them I could possibly die. Without having this [dialysis] plus my medication, I wouldn't last more than two or three weeks." (P21, male, 84 years, PSR AD)
	"Keeps me alive. I want to stay alive. Simple as that." (P25, male, 72 years, PSR AD)
Attitude	
- Positive attitude	*"I don't mind taking them [medicines]. It's better than being, making them worse if you don't, so."* (P10, female, 53 years, PSR AD)
	"They [medicines] are here to be taken, so I take them." (P11, male, 84 years, PSR AD)
	"I always take them, all the time. No matter what, I never stop taking medication. Only what I've been prescribed, I don't take any other medication." (P15, male, 78 years, PSR AD)
	"I got to take them as they keep me healthy. And I don't have a problem with it." (P21, male, 84 years, PSR AD)
	"[medicines] are to my benefit to take them as prescribed." (P21, male, 84 years, PSR AD)
	"It's there to take it, you take it. So I don't have any problem with that." (P24, male, 72 years, PSR AD)
	"They got to take and you take them. Once you start getting sick, they are part of your daily life." (P24, male, 72 years, PSR AD)
	"If they are prescribed for me, I take them." (P28, male, 75 years, PSR AD)
	"You got to take them so you take them… If I don't have it, I suffer." (P28, male, 75 years, PSR AD)
- General dislike	*"I don't like the fact that I need to take them… Not happy about taking medications but the alternatives not good."* (P13, female, 63 years, PSR NAD)
Self-efficacy	
- Disruption to daily routine	*"Well it's in the morning and night, I'm just used to doing that. It's the middle one I have to take care of… I take it at night. Take two at night instead of three, spreading three during the day, which the doctor asked me to try, because it might be more effective. I haven't yet succeeded."* (P8, male, 71 years, PSR NAD)
	"I had my wife been on the hospital, and I had been doing things for her and there's a lot of running around, and just a midday gets left out, so pretty low in the list of priority so, at the moment." (P18, male, 71 years, PSR NAD)
- Inconvenience during travel	*"When I'm camping, you know there's a lot to do, it's just this one extra job in the morning to, you know, wake up in the little tent in the sleeping bag and have to find my pill."* (P3, male, 44 years, PSR NAD)
	"People don't make it difficult for me, but it's the fact that I've, I travel, I like to travel of course make it difficult, because I've got to take all the stuffs with me, organise something every day or whatever. Yes, traveling." (P6, female, 74 years, PSR NAD)
- Accustomed regimen	*"I got all these medications every day, morning, evening, night. So, I never forget it, now."* (P15, male, 78 years, PSR AD)

Themes based on WHO taxonomy	Exemplar quotes
	"Just habit, yeah. In other words, whenever I have my breakfast, my tea, all the time they're there." (P16, male, 65 years, PSR AD)
	"I have been taking them for a long time, that's normal for me. Daily routine." (P20, male, 80 years, PSR AD)
	"They are just part of my life. For last 9 years now, I've been taking them and I've been accustomed to it." (P21, male, 84 years, PSR AD)
	"I've been taking it for a long time and it's just natural." (P27, male, 79 years, PSR AD)
	"I just follow them… [medicines] just normal part of my life." (P30, male, 87 years, PSR A)
- Unaccustomed regimen	*"I'm supposed to take a medicine for my [restless leg], but I keep forgetting… So, um, I've only been told this few days ago and I haven't got used to it, to taking it."* (P8, male, 71 years, PSR NAD)
Action control	
- Forgetfulness	*"I got some magnesium for cramps, but I forget to take them. I'm also supposed to be taking vitamin D but I hardly ever do. That's one of those I forget."* (P8, male, 71 years, PSR NAD)
	"It's just that a little forgetful. I've put it out at the old age… The only worry is to remember to take them." (P14, male, 83 years, PSR NAD)
	"Well, I think that I'm much more, I don't know, forgetful then I used to be, I can't think this clearly, yeah, it's just a fix with, which seems I pick but I don't. Um. Remembering to take it. I think that's the biggest thing." (P6, female, 74 years, PSR NAD)
- Stimuli or cues for action	*"I have a little pill boxes, it holds all morning, noon and night… I just take whatever is required during dinner, or at meal in the night."* (P15, male, 78 years, PSR AD)
	"I have a pill box now. So, I don't need to worry about remembering. That's the main issue." (P18, male, 71 Years, PSR NAD)
	"I've got a dosette box. It's got bed time, lunch, and morning" (P25, male, 72 years, PSR AD)
- Visual allocation of pills	*"I've got them [medicines] in the kitchen table, so I can't forget."* (P10, female, 53 years, PSR AD)
	"Some of the capsules that I'm on, are on my shelves, taking them all in the morning. On dialysis days, I make sure I leave them and take them when I get home, coz otherwise they just washed forever." (P12, female, 80 years, PSR AD)
- Association with meals	*"If I don't have lunch, I don't remember my medicines, always. Lunch is sort of tied to the medicines. So, if I wouldn't eat, I wouldn't take the medicines so regularly, I think."* (P6, female, 74 years, PSR NAD)
Facilitation	
- Role of support	*"I'm retired. I've been looked after. Yes, by my daughter. My daughter does all those [medications] for my side and I've to put them."* (P12, female, 80 years, PSR AD)
	"My wife manages everything. She manages everything. She knows. She's always done it. Ever since I started taking tablets, she looks after it. She knows what medications, what I'm supposed to do and not supposed to do. You know, she put my tablets at every meal and she's been doing that for last 14 years. Ever since I had my kidney out." (P15, male, 78 years, PSR AD)

Themes based on WHO taxonomy	Exemplar quotes
	"If I forget to take them, my wife lets me know… She handles all." (P21, male, 84 years, PSR AD)
	"My wife makes sure I take them... she helps. She gets all medicines ready, tablets ready… she does all, mostly." (P27, male, 79 years, PSR AD)
	"I all live by myself so, just me, I've got to worry about my sickness… It's just me, yeah." (P2, male, 61 years, PSR NAD)
	"Some medicines make me dizzy. It is a problem. Especially when I get no support at home. Coz my husband, he works at night, and I got to be careful. Coz I got no support at home." (P7, female, 65 years, PSR NAD)
Health system/ HCT-related factors	
Quality of interaction with HCT	
- One-way communication	*"[Asking Dr about the need of so many medicines…] I saw doctor at the clinic last time and he said, "No, they are all good". He went through one by one [medicines] and no, that's good, you need that, you need that, so…"* (P7, female, 65 years, PSR NAD)
- Lack of engagement	*"[Consultations are] never very long usually, you know. Just checks the figures, just look at your blood figures and everything's ok and you know."* (P2, male, 61 years, PSR NAD)
	"Not usually. Unless I've a particular problem like my Gout is worse or I'm feeling more depressed. Um, otherwise no. it's [consultation] all very routine." (P4, male, 56 years, PSR NAD)
- Lack of time	*"I really need to speak to the pharmacist. Um, but they're very busy, but I will, I must speak to, I want to know what every medicines, especially 12 medicines in the morning are for."* (P5, female, 58 years, PSR NAD)
- Support from HCT	*"You know, just, give all your tablets to the chemist and he'll sort them out. Makes it so much easier. Coz, he puts them in a pack, a plastic bag [Webster-Pak], um, and he get it for two weeks and you got a just twist and pop a tablets, all those ones you gonna take, so I don't need to get worry about what one of this, one of this, anymore."* (P16, male, 65 years, PSR AD)
	"It's always great with my GP. I've been going to him for 15 years and we're quite informal and he's very helpful and if I complained about what these things, he investigates them properly." (P11, male, 84 years, PSR AD)
Mistrust and collateral arrangements	
- Pressure to hide	*"I forgot to say to him [doctor] about it [not taking phosphate binders]. Because, I think what they will gonna tell me is, I have to take it. I'm frightened obvious the doctor's gonna say, which they probably will, because it's very important, the phosphate, I know that."* (P5, female, 58 years, PSR NAD)
	"I did say the kidney doctor months ago, if they [medicines] were helping remove the fluid, um, because I still have a lot of fluid, and he said just keep taking them, you know, and don't worry about that, you need to keep taking them so, even if it helps a little bit." (P5, female, 58 years, PSR NAD)
- Being a good patient	*"I just take them because, that I'm following the doctor's instructions, I don't… Well, he has his own agenda and he usually takes control of the situation, all them."* (P6, female, 74 years, PSR NAD)
	"I don't. I don't know I take it because I've been told to take it, and I do that. But I don't take it very seriously. And if I miss it, I don't get panic, so." (P8, male, 71 years, PSR NAD)

Themes based on WHO taxonomy	Exemplar quotes
- Personal control of treatment	*"I used to be on Lipitor and stuffs like that, now I don't use them. I don't think I agree with the doctor… I didn't like those… had made me problems… also doctors don't put me on Magnesium, I just put myself on it."* (P2, male, 61 years, PSR NAD)
	"I discuss it with myself. Or, I go to them [doctor] who gets upset because I decide to take more than what I'm prescribed. Yeah, like the Sifrol, it wasn't holding, so I lifted the thing [dose] up to two. And I checked it out [in the internet] and it was okay to do that and then she [doctor] got most upset because she said it effects the kidney, and I said well they're pretty shot already, and she said they can always get worse." (P8, male, 71 years, PSR NAD)
	"Because the doses are too, too [high]…, they have got to decrease it. Coz, I'm taking one tablet, and then they took me off and put it on the other one, and the other one they put me on was too high. Makes me dizzy. So I didn't take anymore." (P7, female, 65 years, PSR NAD)
	"I'm supposed to take it [blood pressure medicine] every day but, I've been taking it every second or third day because of the, coz my blood pressure really low. So, so far I've been able to control at that way. So I decided to stop, if I can do without it, I will… I don't take it terribly seriously." (P8, male, 71 years, PSR NAD)
- Trust in HCT	*"I take my medicines. They give me the right thing, so I just take them. Except when I'm allergic to."* (P10, female, 53 years, PSR AD)
	"I'm consistent about it. Because I've got to take them daily or as prescribed, so I always do as I'm told." (P11, male, 84 years, PSR AD)
	"My doctor is a gentleman and the scholar. He is in charge of it, and he put me in these medication, I take." (P15, male, 78 years, PSR AD)
	"That's what doctor prescribes and I take them." (P20, male, 80 years, PSR AD)
	"I keep taking them until my doctor takes me out of it. I just take the dose that's on the charts I got." (P25, male, 72 years, PSR AD)
Therapy-related factors	
Physical characteristics of medicines	
- Pill size	*"I've got the one [medicine], got to cut it half, I've got a cut five or six in half so I've got half for in the morning and half at night."* (P9, female, 63 years, PSR NAD)
	"I can't take the big ones. The size of the [phosphate binders], sometimes I vomit in backyard. I can't handle big tablets. Large tablet size, too hard, yes, to swallow. Yeah." (P10, female, 53 years, PSR AD)
- Palatability	*"Some of them, as soon as you get them on the tongue, I think that, why not take… I swear it, dissolves straight away and it tastes disgusting! First thing in the morning they, oh! You know, then try to get the water, buff! Just bitter, you know, one of them."* (P5, female, 58 years, PSR NAD)
	"Apart from anything else, some of them taste absolutely disgusting… especially, when the ones like the Allopurinol where you've got them to cut in half, they taste pretty disgusting." (P13, female, 63 years, PSR NAD)
	"There was one tablet that taste like a lolly, and now they don't. They have changed the medicine." (P22, male, 65 years, PSR NAD)
Medicine packaging	*"One I have very hard to get it out. A little capsule, that for pain. Yeah. Very hard to put out. The capsules are completely crushed by the time it gets out of its thing! That's the only problem."* (P11, male, 84 years, PSR AD)

Themes based on WHO taxonomy	Exemplar quotes
Side effects of medicines	*"Sometimes they work, sometimes they really make me sick. Makes me dizzy. Coz it's a bit stronger. I don't take them. Well, if they are not too strong, I'll take them. I always take my medicines, but if they will make me dizzy, I don't."* (P7, female, 65 years, PSR NAD)
	"I know, when I don't take them, I feel better. That feel so severe, vomiting and nausea… so, when I was taking [phosphate binders] it was quite severe… so, I thought no to horrible thing!" (P5, female, 58 years, PSR NAD)
	"I don't like taking them, the [antibiotics], they give me toilet all the time." (P29, male, 65 years, PSR NAD)
Social/ economic factors	
Access to medicines	
- Acquiring script	*"I was hoping if someone can bring those [scripts] here at dialysis unit, so I can just pick them up, when I'm on dialysis. It would be lot easier."* (P2, male, 61 years, PSR NAD)
	"The only hassle is, as far as [blood pressure medicine] is concerned, its supply is only 25 days, so I have to keep asking for repeat." (P23, male, 86 years, PSR NAD)
	"I'm taking a lot of pain tablets at the moment. Finger's pain at all time. I was taking patches, but you can't get it more than a month's supply. So, that means going back on doctors, and when I get out of here [dialysis], I don't want have to go waiting, in a waiting room to get to the doctors on my days off [from dialysis], so I'm just taking Panadol and Panadol with Codeine. But, is not really enough, to be honest." (P2, male, 61 years, PSR NAD)
- Clinic and pharmacy location	*"Because I live out of town, I live an hour out of Hobart, and about 40 minutes from the chemist, just kind of be aware how many more medicines I've got, it's nothing worse than running out and having to drive especially for that, yeah."* (P3, male, 44 years, PSR NAD)
	"Some of the scripts you can't get from pharmacy [local pharmacy]. So, I've had issues actually getting them in the past… When my doctor goes on holidays, I can't acquire a script without doing it a 100 km drive. They [dialysis staffs] refused to help me, and the public doctors refused to give me scripts over the phone. I can't acquire a script over the phone. So I got a drive, do a 100 km drive just to get a script from the public doctors." (P1, male, 53 years, PSR NAD)
Relative affordability	*"Well, they're quite expensive! So they do affect me, the cost. I don't have a health care card. I've to pay the full subsidised price… I've retired and so I'm living of an allocated pension from my superannuation."* (P4, male, 56 years, PSR NAD)
	"The only thing that worries me is, coz I'm in a wheel chair and I need to get to the hospital to get the scripts, it means for $ 30 to get in the taxi to go in there and pick up the script or I drive my mobility scooter all the way in there, which means two hours and an hour of each waiting to pick them up." (P2, male, 61 years, PSR NAD)
	"It's mainly because it costs me a lot of money every month… it is very expensive… I think I take 12 [medications]. It's mainly the expense of the medications. I added it up the other day, for one month... Sixty-a-dollars, sometimes it varies." (P5, female, 58 years, PSR NAD)
Condition-related factors	

Themes based on WHO taxonomy	Exemplar quotes
Symptom severity	*"Have you seen me 12 months ago, I am on a 100 % better [condition] after this year but last year and a year before, no, I didn't really think I'm gonna make it. Not even everybody else also gonna make it either."* (P12, female, 80 years, PSR AD)
	"I don't notice any [improvement] from my medications, whatsoever." (P1, male, 53 years, PSR NAD)

Abbreviations: AD, Adherent; NAD, nonadherent; HCT, healthcare team; PSR, patient self-reports

[μ] Patient-related factors further classified based on adherence support taxonomy by de Bruin *et al*., 2010.

Appendix 10. STROBE Checklist: Pharmacist Survey

	Item No	Recommendation	Reported in section
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title, Abstract and Methods
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any pre-specified hypotheses	Introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Methods, Study design
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Setting and recruitment of participants
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Setting and recruitment of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, Data collection
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Data collection
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Setting and recruitment of

	Item No	Recommendation	Reported in section
			participants; Data collection
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Statistical analysis
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Statistical analysis
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 2; Fig 1; Fig 2
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	

	Item No	Recommendation	Reported in section
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorised	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Study limitations
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 11. Survey Questionnaire: Renal Professionals

Instructions

1. This survey contains **seven sections** and will take about 10-15 minutes to complete. If you do not wish to answer a question or if it does not apply to you, please leave your answer blank.
2. "Adherence" in this survey is defined as the extent to which patients take medications as prescribed by their healthcare providers. Similarly, "nonadherence" refers to number of doses not taken or taken incorrectly that can adversely affect the patient's therapeutic outcomes.
3. Please complete this paper-based survey and return it in the reply-paid envelope provided.

Section 1. Demographic information

1. Profession: [ ] Doctor [ ] Nurse [ ] Pharmacist
   [ ] Other (please specify): _____

2. Designation: [ ] Nurse Unit Manager [ ] Registered Nurse
   [ ] Enrolled Nurse [ ] Pharmacist (not specific)
   [ ] Renal Pharmacist [ ] Intern
   [ ] Registrar [ ] Consultant
   [ ] Resident [ ] Other (please specify): _____

3. Age: _____ 4. Gender: _____ 5. Highest degree achieved: _____

6. Years of post-registration: _____ 7. Years of experience (renal unit): ____

8. State: [ ] TAS [ ] NSW [ ] VIC [ ] NT [ ] ACT
[ ] WA [ ] QLD [ ] SA

9. Dialysis unit location: [ ] Metropolitan
[ ] Rural

10. Organisation type: [ ] Public [ ] Private

11. Size of dialysis unit:
Number of dialysis chairs/ beds/ stations: _____
Number of Full time equivalent (FTE) of Dialysis Nurse: _____

12. Presence of Nursing educator: [ ] Yes
[ ] No
If yes,
% of FTE of service (0.1 – 1.0 FTE): _____

13. Presence of pharmacist in renal unit: [ ] Yes
[ ] No
If yes,
% of FTE of service (0.1 – 1.0 FTE): _____

14. Types of modalities delivered (select all that apply):

[ ] In-centre daytime haemodialysis [ ] In-centre nocturnal haemodialysis

[ ] Home haemodialysis [ ] Peritoneal dialysis

Section 2. Perceived prevalence of medication nonadherence

*Please circle the number that best represents your perception about prevalence of medication nonadherence, where **1** means you **strongly disagree**, and **10** means you **strongly agree** with the following statements:*

Based on my observations in practice, I believe that patients in my unit:	Strongly Disagree — Strongly Agree
1. Have limited understanding of their medications.	1----2----3----4----5----6----7----8----9----10
2. Rarely ask questions about their medications.	1----2----3----4----5----6----7----8----9----10
3. Do not take their medications as prescribed.	1----2----3----4----5----6----7----8----9----10
4. Stop taking some medications when they feel better (for e.g. blood pressure, phosphate binders).	1----2----3----4----5----6----7----8----9----10
5. Are often confused about their medicines.	1----2----3----4----5----6----7----8----9----10
6. Change their dose/dosing interval that suits their lifestyles.	1----2----3----4----5----6----7----8----9----10
7. Express difficulty in swallowing larger pills.	1----2----3----4----5----6----7----8----9----10
8. Do not believe their current medicines are helping them.	1----2----3----4----5----6----7----8----9----10
9. Can't answer questions about their current medications.	1----2----3----4----5----6----7----8----9----10
10. Forget to take their medications sometimes.	1----2----3----4----5----6----7----8----9----10

Please use the following space to provide any other comments, suggestions or opinions about the prevalence of medication nonadherence in your centre:

……

……

……..

Section 3. Perceived contributors of medication nonadherence

*Please circle the number that best represents your perception about contributors of medication nonadherence, where **1** means you **strongly disagree**, and **10** means you **strongly agree** with the following statements:*

Based on my understanding in practice, I believe the following contribute to nonadherence:	Strongly Disagree — Strongly Agree
1. Older patients are more nonadherent than younger patients.	1----2----3----4----5----6----7----8----9----10
2. Male patients are more nonadherent than female.	1----2----3----4----5----6----7----8----9----10
3. Patients with multiple co-morbidities (blood pressure, heart disease, diabetes etc.).	1----2----3----4----5----6----7----8----9----10
4. Patients lacking family/ social support.	1----2----3----4----5----6----7----8----9----10
5. Patients having low income.	1----2----3----4----5----6----7----8----9----10
6. Patients having low level education background (≤ high school).	1----2----3----4----5----6----7----8----9----10
7. Patients having different language/cultural background (non-English speakers or migrants).	1----2----3----4----5----6----7----8----9----10
8. Patient who have limited understanding of their disease state.	1----2----3----4----5----6----7----8----9----10
9. Patients who are not satisfied with their treatment or care they are receiving.	1----2----3----4----5----6----7----8----9----10
10. Patients with complex medication regimens (injections, too many pills etc.).	1----2----3----4----5----6----7----8----9----10

Please use the following space to provide any other comments, suggestions or opinions about the factors contributing medication nonadherence:

……

……

……..

Section 4. Perceived effectiveness of methods that identify medication nonadherence

*Please circle the number that best represents your perception about effective methods of identifying nonadherence, where **1** means **least effective**, and **10** means **most effective** method of identifying nonadherence:*

Based on my understanding in practice, I believe the following are effective in identifying nonadherence:	Least Effective Most Effective
1. Interviewing patients to obtain medication history.	1----2----3----4----5----6----7----8----9----10
2. Asking a patient's family/ carer/ spouse about their medication.	1----2----3----4----5----6----7----8----9----10
3. Objective measures such as serum phosphate levels or blood pressure to see if they are taking medicines.	1----2----3----4----5----6----7----8----9----10
4. Asking patients to bring their medications and count them.	1----2----3----4----5----6----7----8----9----10
5. Having a dedicated healthcare professional (Nurse/ Doctor/ Pharmacist) to take medication history.	1----2----3----4----5----6----7----8----9----10
6. Including a pharmacist in medication reviews and reconciliation.	1----2----3----4----5----6----7----8----9----10

Please use the following space to provide any other comments, suggestions or opinions about the effective methods to identify medication nonadherence:

……

……

……..

Section 5. Barriers to assessing medication nonadherence

*Please circle the number that best represents your opinion about barriers to assessing nonadherence, where **1** means you **strongly disagree**, and **10** means you **strongly agree** with the following statements:*

Barriers	Strongly Disagree — Strongly Agree
1. I don't have knowledge and skills to assess nonadherence in my patients.	1----2----3----4----5----6----7----8----9----10
2. I don't have time to undertake activities that improves adherence.	1----2----3----4----5----6----7----8----9----10
3. I don't think it is my role.	1----2----3----4----5----6----7----8----9----10
4. I think patients are not interested in discussing medication related issues with me.	1----2----3----4----5----6----7----8----9----10
5. There is no support from hospital administration on conducting such activity.	1----2----3----4----5----6----7----8----9----10
6. I have never given a thought about adherence before this survey.	1----2----3----4----5----6----7----8----9----10

Please use the following space to provide any other comments, suggestions or opinions about the barriers to counselling on medication adherence:

……

……

……..

Section 6. Participants' confidence in identifying medication nonadherence

*Please circle the number that best reflect your confidence in identifying medication nonadherence, where **1** means you are **not at all confident**, and **10** means you are **highly confident** in identifying nonadherence:*

How confident do you feel in the following situations?	Not at all Confident Highly Confident
1. Ability to conduct a medication history interview.	1----2----3----4----5----6----7----8----9----10
2. Ability to provide medication counselling.	1----2----3----4----5----6----7----8----9----10
3. Ability to clarify any questions about medications that patients have.	1----2----3----4----5----6----7----8----9----10
4. Ability to suggest strategies to improve adherence.	1----2----3----4----5----6----7----8----9----10
5. Ability to assess patient's knowledge and beliefs about their medications.	1----2----3----4----5----6----7----8----9----10

Section 7. Current practices of assessing medication nonadherence

In the following page, we would like to know the current practices of assessing medication nonadherence in your dialysis unit.

*Please note the scale has been changed and we want a graded response that range from **not applicable** (do not practice at all) to **practice for every patient**.*

Please tick the box (√) that best represent the current practices in your dialysis unit.

Current practices	Not applicable (Do not practice at all)	For some patients (With higher risk of adverse effects)	For most patients (Routine practice except for lower risk patients)	Practice for every patients
1. Interviewing patients to obtain medication history.				
2. Asking a patient's family/ carer/ spouse about their medication.				
3. Objective measures such as serum phosphate levels or blood pressure to see if they are taking medicines.				
4. Asking patients to bring their medications and count them.				
5. Having a dedicated healthcare professional (Nurse/ Doctor/ Pharmacist) to take medication history.				
6. Including a pharmacist in medication reviews and reconciliation.				

Thank you for your participation, the survey is now complete. Please use the following space to provide any other comments, suggestions or opinions about the current practices in your centre:

……

……

……..

---Thank you for taking the time to complete this survey---

Appendix 12. Inter-item correlation matrix and Cronbach's alpha coefficients for psychometric scales: Pharmacist Survey

Prevalence scale	1	2	3	4	5	6	7	8	9	10
1. Have limited understanding of medications	**0.90**									
2. Rarely ask questions about medications	0.77**	**0.91**								
3. Do not take their medications as prescribed	0.54**	0.57**	**0.89**							
4. Stop taking some medications when feel better	0.25	0.29	0.79**	**0.90**						
5. Are often confused about medicines	0.57**	0.49**	0.64**	0.58**	**0.90**					
6. Change dose/dosing interval that suits lifestyles	0.47**	0.38**	0.57**	0.41**	0.65**	**0.90**				
7. Express difficulty in swallowing larger pills	0.46**	0.29	0.53**	0.54**	0.64**	0.55**	**0.91**			
8. Do not believe current medicines are helping them	0.51**	0.52**	0.69**	0.60**	0.53**	0.47**	0.56**	**0.90**		
9. Can't answer questions about current medications	0.65**	0.51**	0.68**	0.53**	0.54**	0.49**	0.35*	0.66**	**0.90**	
10. Forget to take medications sometimes	0.20	0.03	0.55**	0.55**	0.60**	0.53**	0.38*	0.43**	0.46**	**0.91**

Note: Bold values indicates Cronbach's alpha coefficients if item deleted.

**. Correlation is significant at p < 0.01 level (2-tailed).

*. Correlation is significant at p < 0.05 level (2-tailed).

Contributors scale	1	2	3	4	5	6	7	8	9	10
1. Older patients are more nonadherent	**0.77**									
2. Male patients are more nonadherent	0.54**	**0.75**								
3. Patients with multiple co-morbidities	0.23	0.31	**0.71**							
4. Patients lacking family/social support	-0.02	-0.03	0.48**	**0.68**						
5. Patients having low income	0.23	0.21	0.37*	0.53**	**0.71**					
6. Patients having low level education background	-0.01	0.16	0.34	0.42*	0.40*	**0.68**				
7. Having different language/cultural background	-0.19	0.02	-0.07	0.18	-0.19	0.39*	**0.74**			
8. Having limited understanding of disease state	-0.16	-0.13	0.23	0.64**	0.22	0.43*	0.45**	**0.70**		
9. Patients not satisfied with their treatment/care	-0.28	-0.10	0.13	0.42*	0.03	0.34	0.32	0.57**	**0.72**	
10. Patients with complex medication regimens	-0.27	-0.11	0.22	0.75**	0.43*	0.47**	0.31	0.65**	0.67**	**0.68**

Note: Bold values indicates Cronbach's alpha coefficients if item deleted.

**. Correlation is significant at p < 0.01 level (2-tailed).

*. Correlation is significant at p < 0.05 level (2-tailed).

Effectiveness scale	1	2	3	4	5	6
1. Interviewing patients to obtain medication history	**0.48**					
2. Asking patient's family/carer about medication	0.49**	**0.39**				
3. Measuring objective indicators such as SPL/BP	-0.13	0.16	**0.64**			
4. Asking patients to bring medications and count	-0.07	0.22	-0.03	**0.67**		
5. Having a dedicated healthcare professional (Nurse/ Doctor/Pharmacist) to take medication history	0.57**	0.42*	-0.12	0.30	**0.41**	
6. Medication reviews and reconciliation by pharmacist	0.60**	0.41*	0.06	-0.16	0.48**	**0.50**

Note: Bold values indicates Cronbach's alpha coefficients if item deleted.

**. Correlation is significant at p < 0.01 level (2-tailed).

*. Correlation is significant at p < 0.05 level (2-tailed).

Barriers scale	1	2	3	4	5	6
1. Lack of knowledge and skills to assess nonadherence	**0.41**					
2. Lack of time	-0.04	**0.60**				
3. Not my role	0.50**	-0.06	**0.45**			
4. Patient not interested in discussing medication issues	0.46**	0.24	0.54**	**0.35**		
5. No support from hospital administration	0.28	0.02	0.21	0.07	**0.53**	
6. Never thought about adherence before this survey	0.58**	0.13	0.50**	0.51**	0.31	**0.41**

Note: Bold values indicates Cronbach's alpha coefficients if item deleted.

**. Correlation is significant at p < 0.01 level (2-tailed).

*. Correlation is significant at p < 0.05 level (2-tailed).

Confidence scale	1	2	3	4	5
1. Ability to conduct a medication history interview	**0.91**				
2 .Ability to provide medication counselling	0.96**	**0.91**			
3. Ability to clarify patient's medication queries	0.90**	0.93**	**0.90**		
4. Ability to suggest strategies to improve adherence	0.64**	0.67**	0.75**	**0.91**	
5. Ability to assess patient's knowledge and beliefs about medications	0.58**	0.56**	0.65**	0.88**	**0.92**

Note: Bold values indicates Cronbach's alpha coefficients if item deleted.

**. Correlation is significant at p < 0.01 level (2-tailed).

*. Correlation is significant at p < 0.05 level (2-tailed).

Appendix 13. Comments on perceptions and current practices: Pharmacist Survey

Themes	Exemplar quotes
Adjusting to lifestyles	
- Adjusting to lifestyles	Pts are generally good at taking their medications, however will adjust to their lifestyle. For example, phosphate binders 3 times daily with meals. Some patients eat one meal a day so won't take tablets if not eating. P3
- Priority of life events	Is very individual. Even within the same patient, sometimes if things in their life are generally going well then they will cope better with a complex meds regime then if things are not going so well their motivation and therefore adherence drops off. P40
Knowledge and understanding about medicines	
- Limited understanding of medicines	Working with a large population of indigenous patients in remote areas. Most have limited understanding of their medications to limit to "helping kidneys" for their heart or blood sugars. P3
	It's hard to give a definite figure here. Some patients are fantastic with their medications, but there are plenty who have very little understanding of what the agents are for. P8
	Many patients do not understand what the phosphate binders are for. Education is a big focus in our unit. P14
- Lack of tolerability or perceived benefit	Phosphate binders are probably the most prevalent medicines to be not taken correctly - due to lack of tolerability/perceived benefit and understanding. More education time with patients may be a beneficial means to improved compliance and address problems. P4
	Not a strong prevalence but more on ignorance and selective non-compliance, i.e. certain medications are purposely missed if they are perceived as not affecting final outcome. Often they have some understanding then choose what they like. P19
Relative affordability	
	In a low socio-economic town, pts on 20+ dose a day can find difficult affording their medications in the first 5-7 months in the year. P34
Culture and communication barriers	
	Very high level of noncompliance in the Northern Territory. Our patients are largely Indigenous. Language and Cultural barriers in addition to other factors. P11
	Pts rarely ask questions about their tablets due to language barriers or not knowing staff. P3
	I probably find in our centre that it is more prevalent in the aboriginal population, including those who have had to move from remote areas to the city for haemodialysis and have to wait years for a dialysis bed near their regional areas. P39
	NESB and migrants may have poorer comprehension, but are not necessarily more non-compliant by intention. P4
Forgetfulness, role of dose administration aid and support	
- Decreased cognitive function	I think that dialysis affects cognitive function and the patients really can't think properly whilst having treatment. P16
- Role of reminders	All renal patients in the top end receive medications packed into Webster packs so confusion around what to take and when not such a big issue. P3
- Role of support	Family/social support big part of engaging patients in treatment up here. Most dialysis patients separated from their communities forced to live in a strange environment. Often don't cope and don't engage in treatment as a consequence. P3
Role of comorbid illness	
- Tablet burden	Pts have a huge tablet burden which is one of the main reasons for confusion, non-compliance. I have found that by reducing the number of tablets

Themes	Exemplar quotes
	particularly phosphate binders when pts have been prescribed >1 has make a huge difference in their compliance. P17
Need for designated renal pharmacists	
- Lack of designated renal pharmacists	I think our lack of a designated renal pharmacist heavily contributes to the problem. Lack of medication review and thorough medication counselling. P9
	We do not have a pharmacist in the dialysis unit but we have a pharmacist in outpatients that does some of these things for patients including home dialysis pts. P41
	The renal pharmacist at our hospital (1 FTE) looks after the renal ward and inpatient and outpatient dialysis units. Medication review is not performed on all dialysis patients. Only when asked to review them or when we notice there is something that needs following up. This is based in an outpatient unit. As an inpatient, all responses are for every patient. P39
	As mentioned previously I only see hospital inpatients. Cannot comment on practice in the actual dialysis unit which is community run. They have no pharmacy service on site. P33
	The pharmacy has insufficient clinical staff. P24
	No formal pharmacy service funded to our dialysis unit. P20
	There is no funding for a designated renal pharmacist. P8
	Currently we only have a pharmacist who sees patients when they get admitted to the acute hospital setting so all the patients outside of this do not get seen - plans are afoot to remedy this situation. P40
	These factors could be addressed in dedicated medication management reviews. P9
Perceived barriers	
- Lack of time	Time and access (multi-site, patients change dialysis times and 'forgetting' to bring medicines to appointments) are the major barriers. P4
- Staff shortage	I do see that there is generally decent transfer of information, and when patients are admitted directly from dialysis to the hospital their medications are usually reasonably accurate. We have just started an initiative where upon discharge the ward pharmacist will send an updated medication list to the dialysis unit, but sadly this is only one way with present staffing levels. P8
Multidisciplinary role	
	Adherence issues should be everyone's role; pts, carer, doctor, nurse and pharmacist. Very hard if message just from one person. P11
Ongoing education	
	Looking at strategies to improve adherence and nursing students conducting PHD on phosphate binder adherence. P10
Current practices	
	When performing a medication history, I always get the pts to bring in their medicines to ensure we have the correct information. I don't however count them. P17

Note: P = Pharmacist participant (with a number to indicate the participant ID for example, P5 is the fifth respondent).

Appendix 14. STROBE Checklist: Nurses Survey

	Item No	Recommendation	Reported in section
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title, Abstract and Methods
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any pre-specified hypotheses	Introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Methods, Study design
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Setting and recruitment of participants
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Setting and recruitment of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, Data collection
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Data collection
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Setting and recruitment of

	Item No	Recommendation	Reported in section
			participants; Data collection
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Statistical analysis
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Statistical analysis
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 2; Fig 1; Fig 2
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	

	Item No	Recommendation	Reported in section
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorised	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Study limitations
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 15. Inter-item correlation matrix and Cronbach's alpha coefficients for psychometric scales: Nurses Survey

Prevalence scale	1	2	3	4	5	6	7	8	9	10
1. Have limited understanding of medications	**0.85**									
2. Rarely ask questions about medications	0.59**	**0.85**								
3. Do not take their medications as prescribed	0.46**	0.32**	**0.83**							
4. Stop taking some medications when feel better	0.24*	0.17	0.52**	**0.83**						
5. Are often confused about medicines	0.49**	0.50**	0.60**	0.53**	**0.82**					
6. Change dose/dosing interval that suits lifestyles	0.12	0.22*	0.48**	0.37**	0.32**	**0.85**				
7. Express difficulty in swallowing larger pills	-0.06	-0.01	0.35**	0.43**	0.35**	0.29**	**0.86**			
8. Do not believe current medicines are helping them	0.16	0.16	0.30**	0.53**	0.40**	0.28**	0.51**	**0.84**		
9. Can't answer questions about current medications	0.57**	0.46**	0.36**	0.43**	0.71**	0.10	0.21**	0.38**	**0.83**	
10. Forget to take medications sometimes	0.34**	0.26**	0.56**	0.59**	0.58**	0.45**	0.35**	0.43**	0.52**	**0.83**

Note: Bold values indicates Cronbach's alpha coefficients if item deleted.

**. Correlation is significant at p < 0.01 level (2-tailed).

*. Correlation is significant at p < 0.05 level (2-tailed).

Contributors scale	1	2	3	4	5	6	7	8	9	10
1. Older patients are more nonadherent	**0.84**									
2. Male patients are more nonadherent	0.45**	**0.83**								
3. Patients with multiple co-morbidities	0.23*	0.19**	**0.83**							
4. Patients lacking family/social support	0.19*	0.30**	0.30**	**0.80**						
5. Patients having low income	0.21*	0.23*	0.33**	0.67**	**0.81**					
6. Patients having low level education background	0.18	0.33**	0.29**	0.66**	0.67**	**0.80**				
7. Having different language/cultural background	0.06	0.05	0.36**	0.44**	0.38**	0.47**	**0.83**			
8. Having limited understanding of disease state	0.08	0.25**	0.21*	0.64**	0.47**	0.63**	0.38**	**0.81**		
9. Patients not satisfied with their treatment/care	0.09	0.22*	0.04	0.29**	0.15	0.22*	0.16	0.39**	**0.84**	
10. Patients with complex medication regimens	0.13	0.28**	0.39**	0.55**	0.50**	0.49**	0.32**	0.69**	0.45**	**0.80**

Note: Bold values indicates Cronbach's alpha coefficients if item deleted.

**. Correlation is significant at p < 0.01 level (2-tailed).

*. Correlation is significant at p < 0.05 level (2-tailed).

Effectiveness scale	1	2	3	4	5	6
1. Interviewing patients to obtain medication history	**0.66**					
2. Asking patient's family/carer about medication	0.41**	**0.58**				
3. Measuring objective indicators such as SPL/BP	0.17	0.31**	**0.65**			
4. Asking patients to bring medications and count	0.07	0.40**	0.29**	**0.65**		
5. Having a dedicated healthcare professional (Nurse/ Doctor/Pharmacist) to take medication history	0.23*	0.39**	0.18	0.29**	**0.58**	
6. Medication reviews and reconciliation by pharmacist	0.16	0.17	0.09	0.16	0.59**	**0.64**

Note: Bold values indicates Cronbach's alpha coefficients if item deleted.

**. Correlation is significant at p < 0.01 level (2-tailed).

*. Correlation is significant at p < 0.05 level (2-tailed).

Barriers scale	1	2	3	4	5	6
1. Lack of knowledge and skills to assess nonadherence	**0.64**					
2. Lack of time	0.47**	**0.61**				
3. Not my role	0.37**	0.27**	**0.69**			
4. Patient not interested in discussing medication issues	0.22*	0.29**	0.26**	**0.67**		
5. No support from hospital administration	0.43**	0.49**	0.19	0.35**	**0.65**	
6. Never thought about adherence before this survey	0.25**	0.29**	0.19	0.22*	0.05	**0.71**

Note: Bold values indicates Cronbach's alpha coefficients if item deleted.

**. Correlation is significant at p < 0.01 level (2-tailed).

*. Correlation is significant at p < 0.05 level (2-tailed).

Confidence scale	1	2	3	4	5
1. Ability to conduct a medication history interview	**0.88**				
2 .Ability to provide medication counselling	0.74**	**0.87**			
3. Ability to clarify patient's medication queries	0.62**	0.77**	**0.88**		
4. Ability to suggest strategies to improve adherence	0.63**	0.61**	0.60**	**0.89**	
5. Ability to assess patient's knowledge and beliefs about medications	0.63**	0.57**	0.62**	0.72**	**0.89**

Note: Bold values indicates Cronbach's alpha coefficients if item deleted.

**. Correlation is significant at p < 0.01 level (2-tailed).

*. Correlation is significant at p < 0.05 level (2-tailed).

Appendix 16. Comments on perceptions and current practices: Nurses Survey

Themes	Exemplar quotes
Lack of sustainable strategy for empowering self-management	
- Medication self-management	Nonadherence also includes poor management of having their medications available to them at all times, places etc. It is not the patients' intention to be nonadherent. Sometimes it's just difficult to take all medications at all times. In fewer cases, patients intentionally do not take their medication for reasons such as; they think they do not need it, it's not doing anything, they don't know what it's for, or due to the side effects. It's the nurses who may be able to change these latter habits. N104
	Lack of acknowledgment of pts need to have individual self-management strategies and various different approaches to empowering self-management. N94
	Lack of chronic conditions self-management strategies and lack of ability to empower self-management that is truly patient centred (staff). N94
- Adjusting to lifestyles	Mostly younger pts adjust their medications to what suits them or how they feel. N55
	Not taking meds as prescribed is limited i.e. long term younger patients are more likely to adjust tablets i.e. Antihypertensive. N29
- Priority of life events	Stressful home situations mean that their own life is put on hold as they are more worried about others and medications isn't a priority. N14
- Disinterest	Have found that the patients who are most non-adherent, are the ones not interested in learning about them. N93
	They do receive enough education and support from our health system. However, they do not follow instructions or/and are compliable with medications and haemodialysis. N108
- Respect to choice	Some of our home patients make well informed decisions about their medications that we don't necessarily agree with! Sometimes we have to agree amongst ourselves with the medical staff as well, to respect their choices. N18
Knowledge and understanding about medicines	
- Limited understanding of medicines	Some patients do not take phosphate binders correctly - e.g. they don't take with food. The way these are prescribed sometimes says TDS rather than take with food. N19
	Some patient even don't know what medication they are supposed to take. N27
	Often patients need to know that binders need some flexibility according to when they eat. N36
	Our 2 older patients have very little understanding/ interest/ control in their medications. They leave it all to their wives. N41
- Good understanding of medicines	If patients have a good understanding about why they need to take their prescribed medications and the consequences of not doing so, adherence probably increases. Blood results help as then they can see what happens if they don't take their medications and it reinforces the reasons for taking them. N45
	This clinic has all Patients who are interested in their health and well-being. Their understanding to their medication is good. N6
	Pts in our dialysis unit are very informed regarding their medications…. Potential for future transplant used as a motivator. N114
- Lack of tolerability or perceived benefit	Difficult for patients to comprehend well enough that the long term outcomes are worse than taking a large tablet load now i.e. PO_4 binders. N68
	Phosphate binders to be had with meals is often omitted by the patients. N60
	My patients are very empowered about their meds especially binders. N56
	Phosphate binders have the poorest compliance.
	Main problems are with Phosphate binders: Forget, avoid and wrong timing is frequent despite continuing education by dialysis nurses. N37

Themes	Exemplar quotes
	A lot of patients find it difficult to adhere to their phosphate binder regimens. Those with Webster packs are generally compliant, but definitely less knowledgeable about their meds. Non-adherence tends to be higher with phosphate binders. N92
	Generally medications taken as prescribed agent for e.g. phosphate binders and other meds due at 'odd' times during the day. N106
Clinic locations	
- Long waiting times for consultation	As we are a satellite dialysis unit, we do not have a renal doctor on site to answer pts medication questions as they arise. they wait a long time between renal clinic appointments and often forget their questions about medications before they attend. N64
Lack of discharge counselling	
	When patient discharge no clearly explain or remind them any change or what medication they should continuous.
	Lack of health literacy (patients). N94
Professional competence and trust	
- Perceived competence	Many patients will only listen to information about medication compliance from their renal doctor or GP. They do not accept the information from a nurse with the same degree of weight or respect. N64
- Professional trust	Staff attitude is very dictatorial and non-adherence is viewed as 'deviant" thus pts often provide the answers they think the staff wants to hear and the true discussion of why non-adherence occurs hardly ever occurs as pts fear being labelled as 'deviant'. N94
	Pts will frequently tell you they are taking their medicines when in fact they are not. N63
	At times feel the patients just say they forgot or yes I'm taking them, only to see their blood results tells us they are not. N71
Relative affordability	
	The cost of medications is an issue for some, their medicines run out and they don't have any money to buy them. N65
	Pts with low income tend to use old medications before swapping to new prescription due to cost. N103
	People let their scripts run out, don't see a GP to renew them and often tell the dialysis nurse when they have already run out. This is often the case for indigenous patients. N57
	Blister packs are helpful, but many can't/won't pay the extra needed to have them provided. On the other hand, having blister packs often do not help with phosphate binders. Difficult even with a pharmacist input. N8
Prescription refill	Failure to fill script at pharmacy resulting in no medication to be taken. N14
Culture and communication barriers	
	Indigenous status is a good indicator of overall health status. N21
	Increased number of patients live in aged care facility, they receive good care but can cause confusion with duplication and communication regarding medication. N95
Forgetfulness, role of dose administration aid and support	
- Forgetfulness	There is a high number of elderly patients in our unit, a lot of them don't seem to retain much information or forget quite easily what was told to them. N44
	Forgetfulness is a factor. N68
	Patients not always good with memory but if they have meds with them, this might be better. Probably would forget, counting doesn't reveal when or how they took them. N12
- Decreased cognitive function	Regarding limited understanding, it has more to do with their cognitive state, not their knowledge of the disease. N8

Themes	Exemplar quotes
- Role of reminders	Tablet load is a factor. Difficult to generalise here, but people with low education, difficult culture, language etc. are assisted by using dosettes etc. N68
	Patients bringing in medications (Webster packs) do present usually reflect good adherence.
	Webster packs assist. N112
	Getting a copy of Webster pack medication list for people on multiple meds/elderly/memory issues. N93
Role of comorbid illness	
- Comorbid illness	Diabetics seem to be the most affected by non-adherence. N31
	Diabetics the most non-compliant with medications. N31
	Often with so many co morbidities medications themselves are making the patients feel unwell. N36
- Tablet burden	Some patient's express frustration at having to take so many tablets, especially phosphate binders. N45
	Large pill load doesn't help. N65
	Many have polypharmacy and this can add to their confusion over medication but also the taking of them, they just would like to sit and eat a meal without having to take a cupful of medicines. N8
	Patients have so many tablets to take. They require large amounts of water to take them (eats into their fluid restriction) Some meds need to be chewed (not palatable). Often meds in blister packs and don't correspond with times meds need to be taken (binders). N79
- Recent changes with medicines	Patients often get confused, particularly when there are dosage changes. Asking them to bring in their medications and to show you what they are taking can highlight variances between what they have been prescribed. N8
Need for designated renal pharmacists	
Lack of designated renal pharmacists	Have been requesting a renal pharmacist for years! N20
	All other department in this hospital have a dedicated pharmacist but not the dialysis unit. N89
	I'm the pharmacist. Much as we would like to have a dedicated healthcare professional to deal with these issues we don't have one. N86
	Rarely see the pharmacist and do not see her giving pts education. N57
	There is no staff development nose attached to my hospital as it was thought we did not need one specific to the dialysis unit. We share the SND from the next ward but they are flat out, stressed and one has just resigned. For a major teaching hospital it is shocking. N57
	Attempting to get a pharmacist for Dialysis... Currently available for inpatients .... Able to contact them, however very limited service... N29
	I often ring pharmacy to check when last obtained. N71
	Don't have a pharmacist connected to unit. N58
	We have an excellent relationship with community pharmacist which potent a use as a resource tool. N56
	Our patients use different pharmacies and our hospital pharmacists does not see our pts. N65
	We don't have a pharmacist on site here, but in other areas where I worked this was very helpful & reassuring to patients. N18
	Ideally dedicated healthcare professionals should be engaged in medication history taking and reviews but doesn't happen in the dialysis unit. Most patients are assessed at clinic or nephrologists' appointments only. N11
	A pharmacist goes through medications if patient has been in hospital. Prior to discharge. Not done routinely with O.P. N79

Themes	Exemplar quotes
	We used to spend a lot of time doing up med profiles and getting patients to bring in their medications and liaising with local pharmacies. This was very time consuming and patients wouldn't bother to tell you when a medication was changed. We now rely on local pharmacies to send a copy of medication profile to us. N16
	Including pharmacist in medication reviews only in inpatients. N13
Perceived barriers	
- Lack of time	Time is poor on a typical nursing shift, particularly as nurses seem to take on every increasing roles and responsibilities. Medication is, however, as essential component of thorough and holistic nursing care. I find that some patients find it boring or repetitive to discuss medications, so perhaps it should not be done too often. N104
- Lack of training	Lack of training for renal nurses in this area. N94
	I have been working in renal system for few years. I have a lot of knowledge of renal medicines. However, I still feel myself need more comprehensive study and in services. There will be helpful to have self-learning package. N108
- Staff shortage	When the above actions are combined, it may make a difference, but difficult to achieve with patient/professional ratios. N104
Multidisciplinary role	
	How to build up the beliefs of medication and is more important haemodialysis will give them better health outcomes. Of course the better health outcome could bring them normal life and enjoy life. I think the social worker should be involved more. N107
	More social worker input and regularly interview and blood tests for patients. N108
- Role of nurse	It is part of the dialysis nurse role to help pts with education and understanding of adherence to medication regimen. N68
	Discussing/liaising/monitoring pts meds/pathology and reporting to RMO as integral part of a renal nurse role. N106
	Need to initiation for nursing staff on coordination whenever medication/dosage/pathology-this info needs to be consistently fed back to the patients. N106
Ongoing education	
	I always talk to my patients regarding their medications and if they take them or not. If I am not sure about any of their medication, I'll search to found out. N15
	We utilise a monthly 'report card' to discuss pathology results and potential to improve outcomes i.e. taking meds at appropriate times... N29
	We take routine blood pre- and post- dialysis every month and then the nurse unit manager, nurse practitioner, pharmacist, and renal nephrologist meet to discuss the results and make any relevant changes to the patient's medications based on these results. The clinical nurse or nurse unit manager then goes to each patient to discuss the blood results and talk about their medications plus adherence to these. N45
Current practices	
	Serum PO_4 and BP are not solely done to check med compliance, but are routinely done on all patients. Poor results act as a flag for checking medications. Interviewing for med history is meant to be done for all patients - not always attended. N93
	Unless symptomatic, medication history not reviewed. Education more likely to change behaviours but not identifying issues unless problem arise. N12
	We ask patients to bring in their meds, but we don't count them to see how many they have taken. We treat them as adults and therefore educate them regarding how and when to take. They have to take some responsibility unless they have other medical/psycho social issues that impact on this. N8

Note: N = Nurse participant (with a number to indicate the participant ID for example, N5 is the fifth respondent).

Appendix 17. COREQ Checklist: Renal Professionals Interview

No. Item	Guide questions/ description	Reported in section/ remarks
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Interviewer/ facilitator	Which author/s conducted the interview or focus group?	Section: Data collection and analysis
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	Remark: SG (Masters); KL, MJ, RLC and STRZ (PhD)
3. Occupation	What was their occupation at the time of the study?	Section: Data collection and analysis
4. Gender	Was the researcher male or female?	Remark: All male
5. Experience and training	What experience or training did the researcher have?	Remark: Researcher were trained in the design and conduct of qualitative research, and have authored qualitative research article in the past.
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	Section: Data collection and analysis. Remark: The interviewer was unknown to the participants prior to study commencement.
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	Section: Data collection and analysis. Remark: Participants were informed of the interviewer's background and expertise, at the beginning of interview.
8. Interviewer characteristics	What characteristics were reported about the interviewer/ facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	Section: SG introduced himself as a researcher and explained the purpose of interview i.e. to explore barriers to assessing adherence, and identify strategies to improve adherence assessment practices in dialysis settings.
Domain 2: Study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	Section: Data collection and analysis
Participant selection		
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	Section: Participants

No. Item	Guide questions/ description	Reported in section/ remarks
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	Section: Participants
12. Sample size	How many participants were in the study?	Section: Participants
13. Non-participation	How many people refused to participate or dropped out? Reasons?	Section: Participants
Setting		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	Section: Data collection and analysis
15. Presence of nonparticipants	Was anyone else present besides the participants and researchers?	Remark: No
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	Section: Participants
Data collection		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Section: Data collection and analysis. Appendix 2.
18. Repeat interviews	Were repeat interviews carried out? If yes, how many?	Remark: Not conducted
19. Audio/ visual recording	Did the research use audio or visual recording to collect the data?	Section: Data collection and analysis
20. Field notes	Were field notes made during and/or after the interview or focus group?	Section: Data collection and analysis
21. Duration	What was the duration of the interviews or focus group?	Section: Data collection and analysis
22. Data saturation	Was data saturation discussed?	Section: Data collection and analysis
23. Transcripts returned	Were transcripts returned to participants for comment and/ or correction?	Remark: No
Domain 3: Analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	Section: Data collection and analysis
25. Description of the coding tree	Did authors provide a description of the coding tree?	Remark: No. Intermediate documentation is available upon request.
26. Derivation of themes	Were themes identified in advance or derived from the data?	Section: Data collection and analysis
27. Software	What software, if applicable, was used to manage the data?	Section: Data collection and analysis
28. Participant checking	Did participants provide feedback on the findings?	Remark: No
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes/ findings? Was each quotation identified? e.g. participant number	Section: Results. Appendix 3 & 4.

No. Item	Guide questions/ description	Reported in section/ remarks
30. Data and findings consistent	Was there consistency between the data presented and the findings?	Remark: Yes
31. Clarity of major themes	Were major themes clearly presented in the findings?	Section: Results
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Section: Results

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357.

Appendix 18. Interview Guide: Renal Professionals

Interview guide

Hi [name of participant],

Thank you for participating in this study. Our aim is to understand how you assess medication-related issues in dialysis patients and any problems you experience in your practice. Please feel free to add any comments during the discussion to clarify things. As stated on the information and consent form, this session will be recorded, but confidentiality will be maintained at all times. Do you have any questions before we begin?

Before we start, may I ask some of the demographic details from you?

- Age, Gender, Profession/ designation, Year of experience in renal unit, State, Unit location (metro/ rural), Type (public/ private), Number of dialysis chairs, Number of FTE nurse/pharmacist, Modalities delivered

Section 1: Opinion on patients' concerns about medicines

From interviews I conducted with some patients, it seems that some patients don't feel comfortable openly asking questions of their health professionals.

Q. In your experience, is this something you've noticed in your practice? If so, what do you think could be the reasons? Why?

Q. Do you think there is enough time for you to sit with them and answer some of their questions?

Q. What do you think about the trust that patient have in their health care professionals in today's work place environment?

Q. In your experience working with dialysis patients, how well do you think they know about their disease/medications? Could you elaborate.

PROMPT: Do you think they know why they are taking all these pills or do you think they know how to manage their disease well?

Q. In your opinion, how do patients' perceptions about their medicines influence their medication-taking behaviour?

We all know about clinical effectiveness of medicines, but there is something like perceived effectiveness that patients might have regarding their medicines.

Section 2: Current Practices of assessing adherence

Now let's talk about your daily routine at work and occasions how you identify medication-related issues in patients.

Q. *Thinking about your typical daily routine at work,*

Could you walk me through how you check the progress of your patients? Or, how you monitor their disease progression, and self-management?

Q. **How do you identify medication-related issues? I mean how do you figure out if someone is not taking their medicines as prescribed?**

For e.g. through formal interview or other informal discussion, observing their charts, lab reports, physical assessments etc.

Q. Do patients actually admit not taking their medicines or it is something implied through observations?

Q. Have patients ever told you about any difficulty they face about taking their medicines or following their treatment?

Q. What is you take on the likely barriers to taking medicines by the patients?

Q. **Are you aware of any formal adherence assessment methods that can identify medication-related issues in patients?**

Broadly speaking, these issues can be assessed objectively by looking at pill count, pharmacy refill, checking lab indices etc. or subjectively through patient interviews or using validated questionnaires.

Q. In your view, how practical do you think these methods are, and what do you believe to be the more practical methods that could be used in your practice?

Q. How effective would you say they are in the short and the long run?

If No, Q. Why do you think [certain methods] are not practical in your setting?

Q. What are the potential ways to address barriers to implement these methods?

Section 3: Practice models

Now I'd like to know your views on some of the practice models that can be used to assess medication-related issues in dialysis patients.

Q. **What is your opinion on introducing medication adherence assessment into practice the way we measure vital signs such as blood pressure, pulse, temperature etc.?**

If NO, Why?

If YES, how could this be implemented/incorporated in your setting?

Let me give you some scenarios,

Q. How appropriate do you think about,

- Asking patients to write down their concerns related to medications and discuss in a regular basis while they wait to finish their dialysis procedure? Or,
- Asking patients to fill up a validated questionnaire to assess medication adherence in a regular basis?
- Conduct on a regular basis, a 24-hour recall history by looking into patient's personal medication list to check if they are taking their medicines properly?

FOLLOW-UP: Who should take this role [dialysis nurses/ renal pharmacists/ renal physicians]?

FOLLOW-UP: What more could be done to ensure that dialysis patients continue to use their medications as prescribed over the long term?

With this we come to an end of this interview. Do you like to add anything? Or anything that is important that we have left out?

Appendix 19. Barriers to assessing medication adherence: Exemplar quotes Renal Professionals

Themes	Exemplar quotes
A. Organisational barriers	
Theme: Prioritisation of resources	It depends on the organisational priorities. If they are supportive of this or have a vested interest in this… or something like this, then the organisation is more likely to pursue this, but otherwise if they can't see any value in it, any direct dollar savings then it's unlikely to be pursued. P3
	Well, it's really funny when [hospital administration] change the standards, a lot of the areas they fund them, I see there is a lot in their hospital, who have one [pharmacist], they all got one… how come everybody else got one we still don't, it was insane… N10
	Getting funding for a full-time pharmacist... Here we have two sites, so we need to have some kind of [funding] you know, so both sites [have pharmacists] in them. P2
	The barrier is funding, it's all that money to hire dedicated staffs. N10
	I don't think there will be enough funding to add another staff in the unit. N14
Sub-theme 1: Human resources	
- *Shortage of dedicated professionals*	Oh, human resources… I am a senior pharmacist, but I don't have any juniors on my ward that could do that for me at certain time… one solution would be to have technicians trained in nephrology and then know the things to ask patients about, to get good histories. P4
	Big limitation for conducting such activity is the absence of pharmacist in the unit. We wish to have a dedicated pharmacist in our unit to carry these activities. N7
- *Availability of interpreter services*	Not massively accessible, no… we would wait until they are coming to the ward for another reason for that patients and then we will tackle on. So it is not accessible but you can sort of call on them may be five minutes for different things, you really have to plan it. That is a barrier. Availability of an interpreter services is a barrier in the case of non-English speaking patients. P4
	We do try to use the interpreter services but it's not easily available and it's not always possible. N11
	Getting an interpreter would be useful in some situation, but I have never seen anyone sent to the unit. N13
Sub-theme 2: Infrastructure	
- *Availability of private space or interview room*	Privacy can be an issue because most of our patients sit very close to three other patients and there is no way to go to the staff with anything privately with them and it's um, some people are not very interested in talking about their health issues when other people are listening to them. N11
	In our setting here, we don't have single rooms mostly they are open based, people they can see each other, if I am doing care for other patient they can see that. So probably, that may be one of the reason. N17
	We have got an isolation chair, a room on its own. So if we plan ahead, like we did in advanced care plan and things like that… and put the person in the quite room so they are in private… then they would probably open up more and be more truthful, instead when they are in the main unit where they have been observed by everybody. N18
B. Professionals-related barriers	
Theme 1: Interplay between workload and available time	
Professionals' role, responsibility, and scope of practice	I guess the nurses has a lot of other tasks, jobs and things that they should be doing as well. Sometimes it isn't in her priority… maybe there are other needs that need to get completed on the day, which isn't a good thing to say but that could be the reason... I guess that's the complication… it's not necessarily dedicated part of their role. N12

Themes	Exemplar quotes
	I'm not discerning nursing role, but I am just saying that it's not ideal to have nurses taking histories over above pharmacists, because we know more about the drugs and about the kind of, um, range of drugs. P4
	In our setting where we are, I'd say it has to be a nursing role because there's one pharmacist on site for the whole hospital, and they are not specialist in renal, so I'd say it has to be nurse. We have no doctor on site so it has to be nursing, with an escalation plan if we got issues, which we always do anyway. N18
	we are renal nurses so we are confident with the renal medications, but these guys have got numerous other diseases, in which our knowledge is negligible about them so, so really should be somebody who has a broader range of medication knowledge that can take that on board. N10
	[Patients] have demanded pharmacists and sometimes, I mean pharmacists are knowledgeable but sometimes they are not as knowledgeable, they didn't know renal-related medication which we will be educated in, they have to go and look, you know, follow up…N18
Time constraints	We are lot busier now. I think the morbidity of the patients is getting worse they are more acute. So we do have less time but we make time… to sit with our patients and talk to them. N6
	To be honest, here we don't have much time to talk to or go into deep conversation. We are only four staffs and we have 22 patients in a shift, so we really don't have time to go into very deep conversation with them. N16
	When we put the patients on, that's not only our duty of care, we have other duties to be attended as well while they are under dialysis machines and the time we are finished with other duty this patient is about to come out from the machine, so we don't really have much time to talk to them. N15
	[Time] is something we wish we had. But, we try to make it our priority when patients come with some issue to discuss. N7
	There would be. If I know they have questions, then there is time. You know, we make that our priority. So yeah, there is time. P4
Workload	No, because the staff would go insane. I think it's, if we are looking for someone to stay full-time, it probable need to swap around about every 8 weeks, because it would have a significant toll in the staff member involved. P2
	It's just more job for us, increases work load. We already have workload and we have our primary patients to take care. Some day when we are on leave the other nurse may have to take charge over our primary patients and that can increase the workload for the day. N15
Access to patients	Unless they come in during the day for a review, if they come in for a special appointment then there might be an opportunity to capture them, but this could be sometimes missed or just the timing doesn't allow for pharmacists to see them on that particular day because of work load issues, so that would be a hidden miss. P3
	Quite often, our patients will also travel back home, coz many of our patients are force to come in to Darwin and stay in a metro area when they are quite far away, so they will frequently return home and will go without their medications, so lot of lifestyle issues as well would lead them not taking their tablets. P5
Sub-theme 1: Task prioritisation	If patients have a lot of health matters that are more urgent… if they been experiencing pain or having a lot of fall… or whatever that sounds like it's a new problem that hasn't been looked into then the focus becomes on that, rather than the other aspects, like the medications. Whereas if the person is quite stable than… probably there is more emphasis towards…their medicines. P9
	We do have registrars that come and visit the patients but they don't have a lot of time to spend with, they more deal with issues rather than spending time actually seeing how everyone's going, they will just come and see the problems that they are already facing. N11

Themes	Exemplar quotes
Sub-theme 2: Staff compliance towards assessment service	Staff participation may be poor. Unless it's really concerned with particular patients, or feel we need to monitor, but if we gonna do it for everybody the work load is very high and some of the nurses won't be happy participating with this. They are already pre-occupied with many things to do and may say oh it's not our responsibility. N15
	The nursing staff don't realise how important these kind of things are. We administer medication, our duty is to care patients but it's not compulsory for us to assess adherence, it's more of a pharmacists kind of job. N16
	I think knowing the nurses that I work with there will be some challenges in additional form to be filled out, but if they saw the benefits of doing so then even if it's on a weekly basis would be good. N12
Theme 2: Awareness and training deficits	
Lack of knowledge about formal assessment tools	No, not really. I don't know any formal ones… If I wish to teach, I've got my one to be a formal one coz I think it works throughout well, but it does depend on the patients going to the same pharmacy… I've never heard about any official ones, I think it would be interesting to read about. P4
	I know there are some of [formal tools] around, but to name them I wouldn't be able to… P5
	I'm not aware of any [formal assessment tools], no. Not that I use personally. N6
	No, we didn't really have one previously, no I'm not aware of any [formal tools]. N12
	No, I'm not aware of any formal tool, no… if the patient is confused about what medications they are taking, we ask them to bring their medication from home and we go through them. N14
Lack of training and skills	Nursing staff lacks necessary training and skills. I think definitely, there is room for improvement here in relation to educating the nurses about medication on dialysis or all kidney failure patients. N17
	Nurses given the right education would be able to do it. They are seeing these patients every dialysis day, so they will have more opportunities to assess it, but I think they would need a lot of training and sort of intervention in some ways in order to help them identify what sort of things to look for. P5
	We have a nurse educator… who tries to support us in getting education opportunities. I would say that does not support enough by any means because it's very hard to get time to study while you are at work. And in order to do any study days you need to get private study leave and in our particular unit, over the last eighteen months, we have had a shortage of casual nurses in particular, so it's been impossible to have study days or study leave to really do any sort of renal conference or any other educational things. N11
Theme 3: Concerns around practicality/suitability of adherence tools	
Limitation of assessment tool	
- *Labels a patient*	I think it's good to get a general measure of adherence within patients, but I do find this scaling and labelling of patients to be not adhering to be quite harsh. Um, if you remember some of the ones they use in transplant would definitely look at, you know, if they delayed their dosage greater than 2 hours then that would label the patient to be nonadherent, so I do sometimes find questionnaires do label patients as being nonadherent and its sort of taken as quite a nasty term. P5
- *Not quantifiable*	It's not quite possible in that sense, because it's not that easy to measure and absolutely quantify, the only way you could do that is you physically watch the patient for a week, you know, taking all their dosage… I don't think it's possible. P1
- *Practicality of tools*	I think the practicality is not there to do this. Unless we specifically said to the patients can you please bring in your tablets with you each time, but then we have to dedicate

Themes	Exemplar quotes
	time to making assessment each time to show the patients that we are truly interested in this. P3
	To use a validated questionnaire to our client would be actually quite difficult, coz, I mean you have to use interpreters quite frequently for a lot of our patients and the questions would have to be tailored for our clients. P5
- *Suitability in clinical settings*	I'm doing a research study and part of it requires them to take medications, I check compliance by counting how many tablets are left in their box, but clinically I don't. P9
- *Reliability of tools*	Pill counting, I think is always a disaster. Patients will give it to their dog before they actually come in, and it's also prescriptive, isn't that? P2
	I think the validated questionnaire could be useful but it would really depend… on literacy as well of the patients, depends on who is asking how is asking… because otherwise they will tick the box as what you want to hear. P1
Proper timing for assessment	In a real world [during dialysis] is not the ideal time but that's all we have got because like as I said they won't come in early to talk to you, they won't stay beyond, they just want to go, so they only want to be here minimal. N18
	I think… often they are in dialysis and they don't feel well, so it's not an ideal place to go and do any kind of interview. So at times normally understanding they are trapped there for hours and hours, but often they just don't feel well. So you're not going to taking anything at that point. However, it's better than not doing it at all. P2
	When they coming for dialysis, they come at their appointment time and then we have half an hour to assess the patients, have a chat about how they are going in general, so this is when we can talk about their medication, about general health. N11
	I think, during dialysis is very good time to do at because they are stuck there, they can't be off working or here and there so, its practical to do that but, you'll have to make sure that patients have their medications with them or the list with them. P4
Frequency of assessment	I think something is necessary. I think it's not probably be going to necessary in our field on a daily basis. I think the patients would probably find that too much, but certainly on a monthly basis at least, I think that's a really good idea. N11
	I think formally assessing adherence is a good idea, but how often is it you want to do it? Look, at the satellite unit I work, we do it once a month… it works well. N13
	Yeah, that would benefit, but that would be really very time consuming to ask patients every couple of days, but I think that would be a good way to have a look or assess, but yeah would be quite difficult. P5
C. Patient-related barriers	
Theme 1: Communication of assessment services	
Benefit of assessment	I think most of the patients would be happy to answer the questions definitely, if they see the benefit from it that we care about the medicine they are taking. N12
	There needs to be a business case per together to show the benefits of doing this. And I know anecdotally that patients who I interact with, definitely the next time they come in, they definitely more, um, on the board with their medications and may know what they are taking and what they are not taking, and they have the confidence to say to me look I don't take that one because of this problem. P4
Setting expectations of the assessment	I think that a lot of our patients would feel like they are being treated like children, they would probably feel like their privacy is being invaded if we would start doing that. N11
	It would depend on how it is presented, if it wouldn't be presented in a right way there would be patients who would become upset about why we are asking that question all the time and things like that, and patients feeling of having their privacy invaded puts a lot of significant barriers of trust at the nurses. N11
	No, they like to keep their health to themselves. Some of them they don't like to kind of share may be their past history so much unless they are prompted. Actually more than that they don't relate past history or medical issues to their current life. N14

Themes	Exemplar quotes
Theme 2: Patient participation	
Treatment fatigue	They are so much overseen by medical people and they have so many appointments, and if you ask them if they have any worries they will just say no. I'm not sure that one will work. A lot of them, even if you offer review they go, no everything is fine, I actually don't need to see you. P1
	I think, again, often they are in dialysis and they don't feel well, so it's not an ideal place to go and do any kind of interview. So at times normally understanding they are trapped there for hours and hours, but often they just don't feel well. So you're not gonna taking anything at that point. P2
Patient willingness to participate	People do have free will… even though we are trying to do the best to our patients, they still can go, did I can't be bothered? Then you have to go that point, well that's your decision not anybody else's. P2
	If the patient is truly noncompliant and they don't want to know this information, they might make excuses why they don't bring in their medicines, that they forgot or they were running low, nobody was there to get it dispensed from the pharmacy … so again there is this barrier there. P3
	We can do that but again depends on the patients. Some of the patients are not keen for all these type of questionnaires. They are only concerned about visible gains from their treatment. But some of the patients will be willing to participate. N15
Language barriers	We had quite a few issues in our unit based on different cultural groups, um we do have quite a few non-English speaking patients, basically they speak English but not enough to understand, so that can be a challenge as well. N11
	Language barrier is a huge issue in our unit. We have many non-English speaking patients. N13
Theme 3: Trust	
	It's sad, I think some of them have mistrust about what we tell them, they don't trust that we are telling them the right thing or the truth about the medication what they require. N6
	There are always some patients, who for whatever reason, they are not interested in having a trusting good relationship. They are very private. N11
Patient preference of professionals for consultation	We definitely get requests by the patients who wants to speak with the doctors. Often, patients come to the nurse to ask us to talk to the doctors. We are kind of like the middle person. N13
	I think they sometimes think our lack of knowledge, we are not doctors, also the doctors put them in the medications that we won't know what it does and things like that. They don't look at the nursing expertise in our area… they also don't listen to suggestions. You know, how they take their medications, like with the Caltrate, we suggest how they should take it and, you know, they say the doctors said do this way and they won't take on board with the nursing, also the lack of confidence in the nursing that we would know what they are talking about. N18
	Their GPs knows them the best they always think, so the GPs although he is not specialist in any field in particular, but that's the one they usually go in to rather than the renal physician. And most of our patients are elderly, our average age here is like 75 years so, and they have been in the system for a long time and they know their GPs for long time, so I think because of that they trust them. N18
Fear of judgement	Patients feel that they are going to be judged. That, they should by now know this information, why they are asking now this pointless question, causing time wasting. P3
	I think there is a few reasons why they don't ask and one of them is getting an answer they don't like… they probably don't feel there is a problem… N6

Themes	Exemplar quotes
	I guess, may be fear of getting in trouble, they might feel that we might trouble them for not taking their medicines or not following what doctors has said or they are just worried what doctors or nurses would say, or they might have fear if they could ask any questions to us , I suppose… N12

P = Pharmacist, N = Nurse

Appendix 20. Considerations to improve adherence assessment practices: Exemplar quotes Renal Professionals

Themes	Exemplar quotes
Theme 1: Formalisation of the adherence assessment process	
	It's a great idea! To trigger it, so it becomes normal, it's really normal, this is normal. P2
	That could surely be a good way at least to show the patient that we are formalising the process… and could be a better way to encourage them to take their tablets. More likely, because they think all they ask me interests about me, so questionnaire might be a good way as long as we might be able to really use it. N12
	I think it might be good because everybody then is following the same process. The most senior staff knows what to look for and what to ask and more junior staff might miss something or might not be prompted by something, whereas if you got a tool that it will prompt them to ask like questions or prompt them to follow up on certain things. N18
Theme 2: Integration of process and tools into routine	
Incorporating adherence checklist in routine documentation	Well, our daily treatment sheet has, we already have some checklist we go through, sort of might be a simplest just adding up that one, yeah, having any issues with your tablets or um, yeah. N8
	I think it can be like a tick box. We have a care plan for each patients. So, for e.g. once every six months we check the decline or positive response to treatment so may be with medication formally checking we could have kind of a tick box in the care plan once a month or something. We could possibly have on a care plan a medication check and tick the boxes after conversation with the patients. Not so much the questionnaire but just the prompt to have that conversation with the patients. N14
Organizing scheduled sessions for medication reviews	
- *Monthly medication review and reconciliation*	I guess, we can go through like the monthly assessment of the patients, it includes medications, and we just ask their general medications questions, you know, what medications you are taking and do you understand what they are for, and if you have any problems, that's pretty much all we ask. N6
	Having a monthly meeting to discuss the patients' blood results and we can then highlight the need for an increase or decrease in medication or start something else. N8
- *Monthly report card review*	We started doing a report card for our patients with their blood results and there are some prompts in there like, you know, if your phosphate is too high, and are you taking your binders correctly, you need to take them with your first meal for food. Um, when sevelamer was on the PBS there was a lot of education around that, and yeah with the same sort of thing. Just simple prompts on that report card, we found that that's been quite good and it just gives them a clear, yeah, just makes them very clear to them what effect its gonna have them on their body. N8

Themes	Exemplar quotes
	One of the thing that our staff has created was a patient diary. So in that it went all their blood results and our role is to sit down with them once a month and go through their blood results, and explain what was good and what was bad and ask them how they going. That's being quite a good thing for our unit, it's a way of them being I guess invested in their own health, but also gives us an opportunity to sit down and discuss what's happening with their dialysis treatment as well. A report card that was what it's called the patient report card. N10
Verification of objective evidence	
- *Direct observation of medicines, physical assessment, and questioning*	If the blood pressure is not adjusting the way it should be or if it's too low or too high for some reason then we are always asking first about medications whether they have taken them, how they taking them. N11
	By doing the physical observations, blood pressure, weights, and also they have their monthly blood, so their blood shows lot of things, how they are progressing, how well they are. We also ask our patients their general feeling, how they are feeling, everyday… N12
	Webster pack that got hardly anything taken out of it or completely unopened one makes you wonder, other than that, the boxes dispensed in July should have run out in July and now its November that sort of things tells you, I'm a 100% certain this person does or does not take their medicines. P1
- *Asking patient's local pharmacy*	I'm a great believer of just getting a fax from their community pharmacy and that could be done as an outpatient as well. If we have the resources, we would do that, get a fax from their pharmacy and compare with what they say they are taking, assuming they always go to the same pharmacy. You can say, okay we'll see if it does match, look at the histories from the pharmacy, and get an idea of their adherence. P4
	Lot of scripts are filled at an outside chemist, so we can liaise with chemist and say look what tablets they are taking or get them to bring in there, their packet of medications and see what they are actually taking… N8
- *Refill history*	And I'll see if any of the latest dispensing are more than a month ago, then I'll know well hang on, may be they are not compliant with that medicine, they are not adherent with that medicines because it's been a more than a month ago they have lost, had it dispensed, how can they still be on it. Now it might be a drug with a big pack size like the allopurinol, and I'll allow for that so okay, but hang on that was more than a month ago but that was 100 in a box, so that they probably are still on that, and then I'll go back and back, and this is before I even speak to the patients. P4
	So most patients we keep their prescription in the hospital so we can see when they are running out, and we can put it on another script for them but it doesn't always work, and some people keep their own scripts. So, yeah, some people say oh yeah I'm taking that, another people will say oh haven't, or forgot or run out or yeah. N6
- *Monitoring of blood levels*	Yeah, they don't really discuss their medication with us unless we find something with their blood, you know a lot of them calcium is too high or too low, phosphate too high and then we try and discuss compliance with them then. N8
	I certainly think it's a very accurate way of figuring out whether or not, with the whole clinical picture obviously, you don't want to rely on just one thing but if one does not know about issues going on, then definitely blood results can definitely reflect what's been going on with medications at home. N11
- *Observing side-effects of therapy*	When they have symptoms of the problems, let's say for phosphate, if they become itchy all of a sudden, and we can look at their phosphates increasing than that makes it easier. N6

Themes	Exemplar quotes
	I guess symptoms, if the patients report any symptoms like tiredness or itchiness or things like that we would assess but we don't regularly ask the patients if they taking their medications. N12
	If someone is taking iron tablets, I know the iron tablets makes their poo black or rifampicin or something that makes the urine orange, then I ask them about the side effects and if they are not reporting that side effects than that makes me think also are they taking the medicines. P9
Subjective assessment through patient-centric communication	
- *General discussion on medication issues*	I think that is definitely a good approach to start with, because from this you can say at what level the patient is at, and what their baseline understanding is and this way you know how to target your initiatives, whether you bypass the simple things and go to the more complex things. P3
	We also check how they are feeling generally. We have a sort of a holistic conversation with them in terms of how they are coping in life, because if they are having trouble with other things then they are probably going to be having troubles adhering to medications and keeping themselves healthy, we are keen if they are hemodynamically stable and so forth. N6
- *Asking non-judgemental questions*	You have to be diplomatic of course, you can't accuse them but you can say did you may be stop it for a while, did you doctor stopped it… you have to give the patient a way of admitting low adherence without being shamed, because if you scare patients they will, make up lies. So you have to let them know, it's okay for you to tell me that you don't take these tablets, you can give them excuses to not take it. P4
	One of those things where we can be too abrupt I guess with medication adherence, because mainly adherence or compliance can be construed as being rude or whether we are questioning the patients, so I think we have to treat lightly when we ask such sort of questions, you probably come up with the same problems. N6
- *Building good rapport with patients*	I think the issue particularly as pharmacists, is that they don't understand why we are asking what we are asking. Therefore, the good thing about renal patients is that because they've got a chronic condition they will come back in again and again and so when you see them for the third or fourth time, the trust close because they've met you before, they understand what you are at for, and they understand how useful you can be. P4
	When they are comfortable, they tend to open up a little bit more and talk about what issues they have. Generally they like to share stories amongst each other, so that tends to help sort of identify any issues and then obviously building that rapport takes a while, so that needs to get to know you until comfortable saying their concerns about medications. P5
- *Being a good listener*	I think all aspects of professional health could be slightly more empathic about what they do. Coz, sometimes there is a lack of empathy with somebody who has been coming every day for four years, or three times a day for four years. The empathy drops off. P2
	We have to be more empathetic with our patients, they have a chronic condition and have been taking medicines for a long time, so we should be empathetic towards them and try to understand their concerns. N7
Theme 3: Multidisciplinary support	
Partnering with doctor and nursing staff	I think we need to be involved in multi-disciplinary approach, so we have support from our colleagues, so everybody is on the same page and support its initiatives and therefore the patients gets the consistent message that it's not just the pharmacists hounding them, but it's actually got value and purpose behind it. P3
	We can talk to the dialysis nurses and they can give us a bit of a briefing about the patients whether or not they do take their medications… P5

Themes	Exemplar quotes
	You need pharmacy input and you need medical staff input, and you need to have a clinician champion who is at the absolute top of the chain. You can't do this from a nursing perspectives, we can't do it as pharmacists, it has to be clinician led and it's got a come from the top, or there is no funding, there is no support and nothing to care those guys in the bad times. P2
	Encouraging doctors to discuss patient's medications with them on a regular basis, not just to assume that they understand. N11
	I think if we are having any issues with someone who is just, you know continuing not taking their tablets then we get the renal physicians to have a word to them and he basically just go through the reasons why and what will happen if you don't take them so, yeah… N8
	Their GPs knows them the best they always think, so the GPs although he is not specialist in any field in particular, but that's the one they usually go in to rather than the renal physician. And most of our patients are elderly, our average age here is like 75 years so, and they have been in the system for a long time and they know their GPs for long time, so I think because of that they trust them. N18
Liaising with Interpreters and communication facilitators	
- *Formal or professional interpreters*	Sometimes we get interpreters in, the Chinese and Greek patients although they don't speak English very well, they do understand and have a basic English level, but we do use assistance from interpreters when it requires. P5
	We use interpreters where necessary, if they are the patients with different languages… P1
- *Informal or family interpreters*	We wait for their carers or family to come in who speak their language and we interpret via them. P3
	We try our best. Sometimes who have their family members there who can translate and help with that. N11
- *Liaison staffs for indigenous or non-English speaking patients*	For the indigenous, we have support from the aboriginal liaison staffs so they can talk to her and help in medication management. N12
	[Indigenous patients] rely heavily on the aboriginal co-op so, if they don't know anything they go there and the aboriginal nurse come up to help them, so we liaise with her quite a bit too, in regard to any issues that comes up with those patients. N8

P = Pharmacist, N = Nurse

Appendix 21. Tasmanian Health and Medical HREC Approval

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
Telephone + 61 3 6226 7479
Facsimile + 61 3 6226 7148
Email Human.Ethics@utas.edu.au
www.research.utas.edu.au/human_ethics/

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

02 December 2014

Dr Tabish Razi Zaidi
C/- University of Tasmania

Sent via email

Dear Dr Razi Zaidi

REF NO: H0014506
TITLE: Medication regimen complexity, concordance to prescribed medications and a survey of complementary and alternative medications in haemodialysis patients

Document	***Version***	***Date***
Information Sheet and Consent Form	Version 2	November 2014
Low risk Application	Version 2	November 2014
Medication Regimen Complexity Index		
Patient Medication Interview Questions		
Privacy Form	V1	October 2014
Recruitment Advertisement	Version 2	
Self-administered Questionnaires		

The Tasmanian Health and Medical Human Research Ethics Committee considered and approved the above documentation on **26 November 2014** to be conducted at the following site(s):

Royal Hobart Hospital
Pharmacy, School of Medicine
Dialysis Unit, Nephrology South, Hobart

Please ensure that all investigators involved with this project have cited the approved versions of the documents listed within this letter and use only these versions in conducting this research project.

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approvals of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct in Human Research* (NHMRC 2007 updated 2014).

Therefore, the Chief Investigator's responsibility is to ensure that:

(1) The individual researcher's protocol complies with the HREC approved protocol.

(2) Modifications to the protocol do not proceed until **approval** is obtained in writing from the HREC. Please note that all requests for changes to approved documents must include a version number and date when submitted for review by the HREC.

(3) Section 5.5.3 of the National Statement states:

Researchers have a significant responsibility in monitoring approved research as they are in the best position to observe any adverse events or unexpected outcomes. They should report such events or outcomes promptly to the relevant institution/s and ethical review body/ies and take prompt steps to deal with any unexpected risks.

The appropriate forms for reporting such events in relation to clinical and non-clinical trials and innovations can be located at the website below. All adverse events must be reported regardless of whether or not the event, in your opinion, is a direct effect of the therapeutic goods being tested.
http://www.research.utas.edu.au/human_ethics/medical_forms.htm

(4) All research participants must be provided with the current Patient Information Sheet and Consent Form, unless otherwise approved by the Committee.

(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

(6) This study has approval for 4 years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due 26 November 2015**.** You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 6254.

Yours sincerely

Jude Vienna-Hallam

Digitally signed by Jude Vienna-Hallam
DN: cn=Jude Vienna-Hallam, o=University of Tasmania, ou=Ethics Unit, email=Jude.Vienna-Hallam@utas.edu.au, c=AU
Date: 2014.12.02 14:38:08 +11'00'

Ethics Administrator
Research Integrity and Ethics Unit
Office of Research Services
University of Tasmania
Private Bag 01
Hobart Tas 7001
T +61 3 6226 6254
http://www.utas.edu.au/research-admin/home

Appendix 22. Tasmanian Social Sciences HREC Approval

Social Science Ethics Officer
Private Bag 01 Hobart
Tasmania 7001 Australia
Tel: (03) 6226 2763
Fax: (03) 6226 7148
Katherine.Shaw@utas.edu.au

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

2 December 2015

Dr Tabish Razi Zaidi
Division of Pharmacy
University of Tasmania

Sent via email

Dear Dr Razi Zaidi

Re: MINIMAL RISK ETHICS APPLICATION APPROVAL
Ethics Ref: **H0015433 - Cross-sectional survey of current practices in measuring medication adherence at Australian dialysis centres - a pilot study**

We are pleased to advise that acting on a mandate from the Tasmania Social Sciences HREC, the Chair of the committee considered and approved the above project on 1 December 2015.

This approval constitutes ethical clearance by the Tasmania Social Sciences Human Research Ethics Committee. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approval of other bodies or authorities is required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

Please note that this approval is for four years and is conditional upon receipt of an annual Progress Report. Ethics approval for this project will lapse if a Progress Report is not submitted.

The following conditions apply to this approval. Failure to abide by these conditions may result in suspension or discontinuation of approval.

1. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval, to ensure the project is conducted as approved by the Ethics Committee, and to notify the Committee if any investigators are added to, or cease involvement with, the project.

2. Complaints: If any complaints are received or ethical issues arise during the course of the project, investigators should advise the Executive Officer of the Ethics Committee on 03 6226 7479 or human.ethics@utas.edu.au.

3. Incidents or adverse effects: Investigators should notify the Ethics Committee immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.

4. Amendments to Project: Modifications to the project must not proceed until approval is obtained from the Ethics Committee. Please submit an Amendment Form (available on our website) to notify the Ethics Committee of the proposed modifications.

5. Annual Report: Continued approval for this project is dependent on the submission of a Progress Report by the anniversary date of your approval. You will be sent a courtesy reminder closer to this date. **Failure to submit a Progress Report will mean that ethics approval for this project will lapse.**

6. Final Report: A Final Report and a copy of any published material arising from the project, either in full or abstract, must be provided at the end of the project.

Yours sincerely

Katherine Shaw
Executive Officer
Tasmania Social Sciences HREC

Appendix 23. Invitation Letter for Nurses Survey

UNIVERSITY of TASMANIA

FACULTY OF HEALTH

School of Medicine

Date: 16/02/2016

Dear Nurse Unit Manager,

Medication nonadherence may lead to poor patient outcomes and costs millions of dollars to the healthcare system. As such, I am studying medication adherence in dialysis patients across Australia for my PhD. Dialysis nurses may play a pivotal role in managing dialysis treatment prescriptions and improving dialysis attendance and adherence among patients and their opinions may guide interventions to improve medication adherence.

I would like to invite you to complete an online survey that seek dialysis nurse practitioners' opinions on medication nonadherence, its causes & how it may be improved in patients undergoing dialysis. The survey should take approximately 10-15 minutes to complete, and is available through the link: https://www.pharm.utas.edu.au/surveys/index.php/423245?lang=en

I also need your assistance in forwarding the study invitations to the doctors, nurses and pharmacists involved in patient care at your dialysis unit. Alternatively, we have also send few paper-based copies of survey packs to complete. If you have any general queries regarding this survey, please do not hesitate to contact me at saurav.ghimire@utas.edu.au or Dr Syed Tabish R Zaidi through tabish.razizaidi@utas.edu.au.

I appreciate your time and assistance in promoting our study at your dialysis centre. I will be more than happy to answer any questions that you may have in this regards.

Yours Sincerely,

Saurav Ghimire
PhD Candidate

Dr Syed Tabish R Zaidi
Lecturer in Pharmacy

Appendix 24. Participant Information Sheet for Survey Participants

UNIVERSITY of TASMANIA

FACULTY OF HEALTH

School of Medicine

Participant information sheet [Ver 1.0][20/11/2015]

Project title

Cross-sectional survey of current practices in measuring medication adherence at Australian dialysis centres- a pilot study

Invitation

You have been invited to participate in this survey as you are the healthcare professionals (clinicians, nursing and pharmacy staffs) providing care to the end-stage kidney disease (ESKD) patients undergoing maintenance dialysis treatment at the dialysis centres in Australia.

My name is Saurav Ghimire, and this research has been conducted as part of my PhD research project in Clinical Pharmacy, and in conjunction with my supervisors Dr Tabish Razi Zaidi, Lecturer in Pharmacy, School of Medicine, UTAS and Dr Ronald L Castelino, Lecturer in Therapeutics, Pharmacy, School of Medicine, UTAS and our research collaborators Dr Matthew D Jose, Professor of Medicine, School of Medicine, UTAS and Mr Colin Banks, Nursing Unit Manager, Nephrology South, Royal Hobart Hospital, Hobart, Australia.

What is the purpose of this research?

The aim of this survey and research is to measure healthcare professionals' perception of prevalence and contributors of medication nonadherence among ESKD patients attending dialysis centres, as well as to identify areas of current practices and the barriers to assessing and improving adherence among ESKD patients in dialysis centres in Australia. This research will in turn assist with identifying ways in which medication adherence can be improved among ESKD patients undergoing chronic dialysis treatment.

What will I be asked to do?

You will be asked to complete an online or a paper-based survey (whichever appropriate) which will take approximately 10-15 minutes to complete. The survey will involve questions asking about your perceived knowledge on medication adherence and its consequences on patient's clinical outcomes, what you see as the most important contributors of nonadherence, barriers to assessing and improving medication adherence, areas of current practices in effective medication management, and confidence in accurately assessing and resolving issues related to adherence in your dialysis centres. There will also be a section where you can include other relevant comments. The responses will be completely anonymous, and only the research team members will have access to your answers and results.

Do I have to take part in this research project?

Your involvement in this study is entirely voluntary, and as the results will be de-identified, it will not be possible for either anyone involved in this study or others in the workplace to know your individual responses.

Are they any benefits associated with being in this study?

There is an opportunity to win a prepaid gift voucher worth $100 by eight participants that will be drawn at the conclusion of the survey availability, should you wish to include your contact details in order to be considered for this prize draw. In addition to this, you will be contributing valuable information on critical issues related with medication nonadherence by the dialysis patients, as often adherence research involving patients is not being translated into practice. Hence, the knowledge gained from this study will be used in the future to best tailor medication management practices in dialysis centres to improve medication adherence outcomes.

Are they any risks or cost associated with being in this study?

There are no risks associated with being involved in this study, as the results will be de-identified, and neither those directly involved in the study nor others in either the workplace will be able to link results to individual participants.

What will happen to the information collected when the study is over?

Once the survey is completed from all participants, data gathered from this study will be collated and analysed to determine the overall trends and answers to the study objectives. The results of the study will be de-identified and stored within the university database according to protocols outlined by the university and ethics committee.

How will the results of the study be published?

The results of this study will be published in peer-reviewed journals, however the study results will be de-identified when presenting the findings.

What if I have a complaint or any concerns about the study?

If you have any questions or concerns about any aspect of this study please do not hesitate to contact either myself through email (saurav.ghimire@utas.edu.au) or Dr Tabish Razi Zaidi through email (Tabish.RaziZaidi@utas.edu.au). This study has been approved by the Tasmanian Social Sciences Human Research Ethics Committee. If you have concerns or complaints about the conduct of this study, please contact the Executive Officer of the HREC (Tasmania) Network on +61 3 6226 6254 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. Please quote ethics reference number H0015433. Thank you for taking time to consider this study. This information sheet is for you to keep for your record. If you wish to participate in this study, you may either:

1. Complete a paper-based survey and return it in the reply-paid envelope. Or,
2. Complete an online version of the survey, by entering the URL https://www.pharm.utas.edu.au/surveys/index.php/423245?lang=en into your browser or alternately simply scan the QR code opposite with your smart phone or other QR enabled device to gain access. In both the cases, completion and return of the survey implies consent to participate in the research.

Appendix 25. Participant Information Sheet: Renal Dialysis Patients

UNIVERSITY of TASMANIA

FACULTY OF HEALTH

School of Medicine

PARTICIPANT INFORMATION SHEET

Medication regimen complexity, concordance to prescribed medications and a survey of complementary and alternative medications in haemodialysis patients

Invitation

You are invited to participate in a research study that evaluates the impact of medication complexity on medication taking behaviour and to survey the use of natural medicines by chronic kidney disease patients.

The study is being conducted by Dr Tabish Razi Zaidi, Lecturer in Pharmacy, School of Pharmacy at the University of Tasmania. The other researchers are:

- Professor Matthew Jose, Professor of Medicine, School of Medicine UTAS
- Dr Ronald Castelino, Lecturer in Therapeutics, School of Pharmacy UTAS
- Mr Saurav Ghimire, PhD Candidate, School of Pharmacy UTAS

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. 'What is the purpose of this study?'

The purpose is to investigate the impact of medication complexity on medication taking behaviour and to survey the use of natural medicines by chronic kidney disease patients.

2. 'Why have I been invited to participate in this study?'

You are eligible to participate in this study because you have been identified as fitting the specific criteria of the study, which is;

Adult patient (18 years or over) and currently receiving maintenance dialysis treatment in the outpatient dialysis facility of Royal Hobart Hospital (RHH)/ Nephrology South, New Town, Tasmania.

3. 'What if I don't want to take part in this study, or if I want to withdraw later?'

Participation in this study is voluntary. It is completely up to you whether or not you participate. You will be kept informed of any significant new findings that may affect your willingness to continue in the study. If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason. However, it may not be possible to return or withdraw your data from the study results if these have already had your identifying details removed.

4. 'What does this study involve?'

If you agree to participate in this study, you will be asked to sign the Participant

Consent Form. You will then be interviewed for your medication history that involves your current prescription medicines, non-prescription and herbal medicines. At the end of the interview you will be requested to answer a self-administered questionnaire to obtain information on your health outcomes and perceived burden of medication administration. This will take approximately 30 minutes and can be done at an agreed time between you and the researchers. The accuracy of the medication history provided by you will be verified by reviewing your medication records, inspecting medicines containers (including blister packs) and contacting other prescribers and pharmacist involved in care.

5. 'How is this study being paid for?'

The study is a part of a PhD project and all the cost incurred during the study will be managed by School of Pharmacy, UTAS. No money is paid directly to individual researchers.

6. 'Are there risks to me in taking part in this study?'

All we need is your **convenient time** to talk with us about your medication history. The study does not involve any foreseeable risk to your health and well-being.

7. 'Will I benefit from the study?'

This study will identify unique challenges faced by chronic kidney disease patients in adhering to their complex medication therapy. Therefore, as knowledge is gained after analysis, future interventions aimed at improving the quality use of medicines and drug therapy outcomes can be implemented. However, no immediate benefit from the study can be assured for you.

8. 'Will taking part in this study cost me anything, and will I be paid?

Participation in this study will not cost you anything. Interview sessions will be arranged during your regular visit to dialysis unit.

9. 'How will my confidentiality be protected?'

Only the researchers named above will know whether or not you are participating in this study. Any identifiable information that is collected about you in connection with this study will remain confidential and will be disclosed only with your permission, or except as required by law. Only the researchers named above will have access to your details and results that will be held securely at School of Pharmacy UTAS.

10. 'What happens with the results?'

If you give us your permission by signing the consent document, we plan to present the results at conferences or other professional forums, publish the results in peer-reviewed journals and disclose the results to the sponsor for monitoring purposes and the HREC for monitoring purposes.

In any publication, information will be provided in such a way that you cannot be identified. Results of the study will be provided to you, if you wish.

11. 'What should I do if I want to discuss this study further before I decide?'

When you have read this information, the researcher Saurav Ghimire, will discuss it with you and any queries you may have. If you would like to know more at any stage, please do not hesitate to contact him on 03 6226 1069.

12. 'Who should I contact if I have concerns about the conduct of this study?'

This study has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have concerns or complaints about the conduct of this study should contact the Executive Officer of the HREC (Tasmania) Network on (03) 6226 6254 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. You will need to quote [*HREC number:* H0014506].

Thank you for taking the time to consider this study.

If you wish to take part in it, please sign the attached consent form. This information sheet is for you to keep.

Appendix 26. Consent Form: Renal dialysis Patients

UNIVERSITY of TASMANIA

FACULTY OF HEALTH

School of Medicine

CONSENT FORM

Medication regimen complexity, concordance to prescribed medications and a survey of complementary and alternative medications in haemodialysis patients

1. I acknowledge that the nature, purpose and anticipated effects of the project so far as it affects me, have been fully explained to my satisfaction by the research worker and my consent is given voluntarily.

2. I understand that in order to be eligible for the study, I must be 18 years or above and currently receiving maintenance dialysis treatment in the outpatient dialysis facility of Royal Hobart Hospital (RHH)/ Nephrology South, New Town, Tasmania.

3. The details of the procedure proposed have also been explained to me, including the anticipated length of time it will take, the frequency with which the procedure will be performed, and an indication of any discomfort, which may be expected.

4. I understand that there are the following risks or possible discomfort: No any foreseeable risk to my health and well-being

5. Although I understand that the purpose of this research project is to improve the quality of medical care, it has also been explained that my involvement may not be of any benefit to me.

6. I have been given the opportunity to have a member of my family or friend present while the project was explained to me.

7. I am informed that no information regarding any medical history will be divulged and the results of any tests involving me will not be published so as to reveal my identity.

8. I understand that I will be given a signed copy of this patient information sheet and consent form. I am not giving up my legal rights by signing this consent form.

9. I understand that the study will be conducted in accordance with the latest versions of the *National Statement on Ethical Conduct in Human Research 2007* and applicable privacy laws.

10. Name of participant _____

Signature of participant _____ Date _____

The following section regarding the witness is not essential but may be appropriate for patients where the research teams feel that the participant should have a witness to the consent procedure or where the protocol insists upon witnesses.

Name of witness (if appropriate) _____

Signature of witness _____ Date _____

11. I have explained this project and the implications of participation in it to this volunteer and I believe that the consent is informed and that he/she understands the implications of participation.

Name of investigator _____

Signature of investigator _____ Date _____

Appendix 27. Participant Information Sheet: Renal Professionals Interview

UNIVERSITY of TASMANIA

FACULTY OF HEALTH

School of Medicine

Participant information sheet **[Ver 2.0][10/08/2016]**

This information sheet is for participants who have completed the survey.

Project title

Cross-sectional survey of current practices in measuring medication adherence at Australian dialysis centres- a pilot study

Invitation

You have been invited to participate in this follow-up interview study as you are the healthcare professionals (clinicians, nursing and pharmacy staffs) providing care to the end-stage kidney disease (ESKD) patients undergoing maintenance dialysis treatment at the dialysis centres in Australia.

My name is Saurav Ghimire, and this research has been conducted as part of my PhD research project in Clinical Pharmacy, and in conjunction with my supervisors Dr Syed Tabish Razi Zaidi, Lecturer in Pharmacy, School of Medicine, UTAS and Dr Ronald L Castelino, Lecturer in Therapeutics, Pharmacy, School of Medicine, UTAS and our research collaborators Dr Matthew D Jose, Professor of Medicine, School of Medicine, UTAS and Mr Colin Banks, Nursing Unit Manager, Nephrology South, Royal Hobart Hospital, Hobart, Australia.

What is the purpose of this research?

The aim of this research is to measure healthcare professionals' perception of prevalence and contributors of medication nonadherence among ESKD patients attending dialysis centres, as well as to identify areas of current practices and the barriers to assessing and improving adherence among ESKD patients in dialysis centres in Australia. This research will in turn assist with identifying ways in which medication adherence can be improved among ESKD patients undergoing chronic dialysis treatment.

What will I be asked to do?

You will be asked to participate in a semi-structured one-on-one phone interview that seeks information on current practices and barriers faced by the healthcare professionals while assessing and addressing medication adherence in dialysis patients. This will take between 15-20 minutes and can be done at an agreed time between you and the research team.

Do I have to take part in this research project?

Your involvement in this study is entirely voluntary, and as the results will be de-identified, it will not be possible for either anyone involved in this study or others in the workplace to know your individual response.

Are they any benefits associated with being in this study?

A gratitude prepaid gift voucher worth $50 will be provided for each participants in the follow-up interview study. In addition to this, you will be contributing valuable information on critical issues related with medication nonadherence in the dialysis patients, as often adherence research involving patients is not being translated into practice. Hence, the knowledge gained from this study will be used in the future

to best tailor medication management practices in dialysis centres to improve medication adherence outcomes.

Are they any risks or cost associated with being in this study?

There are no risks associated with being involved in this study, as the results will be de-identified, and neither those directly involved in the study nor others in either the workplace will be able to link results to individual participants.

What will happen to the information collected when the study is over?

Once the study is completed from all participants, data gathered from this study will be collated and analysed to determine the overall trends and answers to the study objectives. The results of the study will be de-identified and stored within the university database according to protocols outlined by the university and ethics committee.

How will the results of the study be published?

The results of this study will be published in peer-reviewed journals, however the study results will be de-identified when presenting the findings.

What if I have a complaint or any concerns about the study?

If you have any questions or concerns about any aspect of this study please do not hesitate to contact either myself through email (saurav.ghimire@utas.edu.au) or Dr Syed Tabish Razi Zaidi through email (Tabish.RaziZaidi@utas.edu.au). This study has been approved by the Tasmanian Social Sciences Human Research Ethics Committee. If you have concerns or complaints about the conduct of this study, please contact the Executive Officer of the HREC (Tasmania) Network on +61 3 6226 6254 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. Please quote ethics reference number H0015433.

Thank you for taking time to consider this study.

This information sheet is for you to keep for your record.

If you wish to participate in this study, please sign the attached consent form.

Appendix 28. Consent Form: Renal Professionals

UNIVERSITY of TASMANIA

FACULTY OF HEALTH

School of Medicine

Participant Consent Form [Ver 2.0] [10/08/2016]

Project title

Cross-sectional survey of current practices in measuring medication adherence at Australian dialysis centres- a pilot study

CONSENT FORM FOR INTERVIEW PARTICIPANTS

1. I agree to take part in the research study named above.
2. I have read and understood the Information Sheet for this study.
3. The nature and possible effects of the study have been explained to me.
4. I understand this study involves participating in an interview that seeks my opinion on medication adherence issues in dialysis patients and will take approximately 15-20 minutes to complete.
5. I understand that participation in this study involves no foreseeable risks.
6. I understand that all research data will be securely stored on the premises of the University of Tasmania for five years from the publication of the study results, and will then be destroyed.
7. Any questions that I have asked have been answered to my satisfaction.
8. I understand that the researcher(s) will maintain confidentiality and that any information I supply to the researcher(s) will be used only for the research.
9. I understand that the study results will be published such that I cannot be identified as a participant.
10. I understand that my participation is voluntary and that I may withdraw at any time without any effect.

Participant's name: _____ Date: _____

Participant's signature: _____

UNIVERSITY of TASMANIA

FACULTY OF HEALTH

School of Medicine

Statement by the Investigator

☐ I have explained the project and the implications of participation in it to this volunteer, and I believe that the consent is informed and that he/she understands the implications of participation.

If the Investigator has not had an opportunity to talk to participants prior to them participating, the following must be ticked.

☒ The participant has received the Information Sheet where my details have been provided so participants have had the opportunity to contact me prior to consenting to participate in this project.

Investigator's name: Saurav Ghimire

Date: 17/10/2016

Investigator's signature:

Appendix 29. Recruitment advertisement: Renal dialysis patients

UNIVERSITY of TASMANIA

We want YOU to talk to us about YOUR MEDICATIONS

"Our purpose is to **identify** various **challenges** you face in managing your **medications**"

Your assistance will **help** us develop better ways to **manage medications** for dialysis patients

What YOU need to tell US?

- ✓ A complete **list** of all **medications** you are using and how much and how often you use them.
- ✓ We also want to hear about any **changes** in your **medications** including any **over the counter** medications, **herbal or natural** medications, **vitamins or nutritional supplements.**

Time commitment?

We will need approx. **half an hour** of your time. We can also talk **during** your dialysis session.

For additional information, please contact

Saurav Ghimire at 03-6226 1069, 0412511306,Email: saurav.ghimire@utas.edu.au

Principal Investigator: Dr. Tabish Razi Zaidi, Pharmacy, School of Medicine, UTAS

Appendix 30. Recruitment advertisement: Renal Professionals

UNIVERSITY of TASMANIA

FACULTY OF HEALTH
School of Medicine

Cross-Sectional Survey of Current Practices in Measuring Medication Adherence at Australian Dialysis Centers- A Pilot Study

Dear

Doctors, Nurses, & Pharmacists,

We need your assistance in understanding the current practices of measuring & promoting medication adherence at your dialysis centers.

We would like to invite you to complete an online survey that measures healthcare professionals' opinions on nonadherence, its causes & how it can be assessed and improved in patients undergoing dialysis treatment.

The survey should take 10-15 minutes to complete, and is available through the following web link: https://www.pharm.utas.edu.au/surveys/index.php/423245?lang=en or simply scan the QR code below. Alternatively, if you would prefer paper-based copies, this can be arranged by simply contacting below.

We appreciate your time and assistance in helping us by participating in this survey.

FOR DETAILS CONTACT
Saurav Ghimire
Private Bag 26, Hobart 7001,
Tasmania, Australia
Phone: 03 6226 1069
Email: saurav.ghimire@utas.edu.au

Participants will have 1 in 8 chances of winning Coles-Myer Gift Cards worth $100.

This study has been approved by the Social Sciences Human Research Ethics Committee (Tasmania) Network. Any ethical concerns, or complaints regarding the conduct of the study can be directed to the Executive Officer, HREC on 03 6226 6254 or email human.ethics@utas.edu.au (Reference No: H15433).